THE CONSTITUTION OF LAUROTETANINE, BOLDINE AND ACTINODAPHNINE.

by

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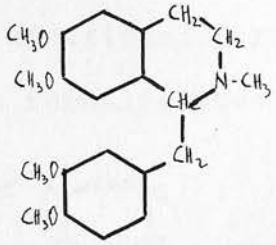
ON APORPHINE ALKALOIDS.

The Constitution of Laurotetanine, Boldine and Actinodaphnine.

Part I. General Introduction.

The term "alkaloid" is generally understood as meaning a relatively complex basic substance occurring naturally and usually possessing some physiological action.

The largest group of the wide field of alkaloids is the so-called isoquinoline group, which contains about ninety different known natural bases. Also morphine, the first alkaloid to be discovered by Sertürner (1) is usually looked upon as belonging to the isoquinoline derivatives. The prototype of the isoquinoline alkaloids is laudanosine,

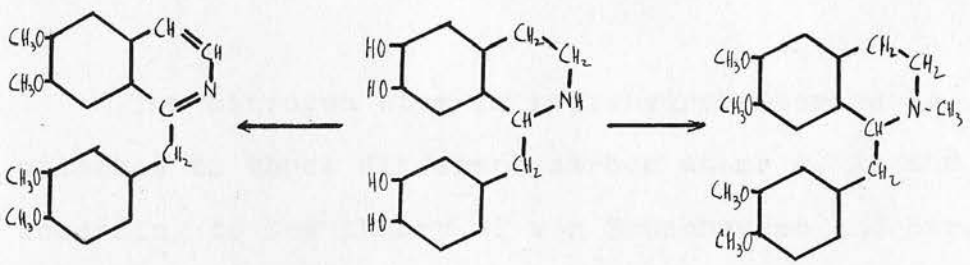


synthesised by Pictet and Maria Finkelstein's classical synthesis in 1909 (2).

From/

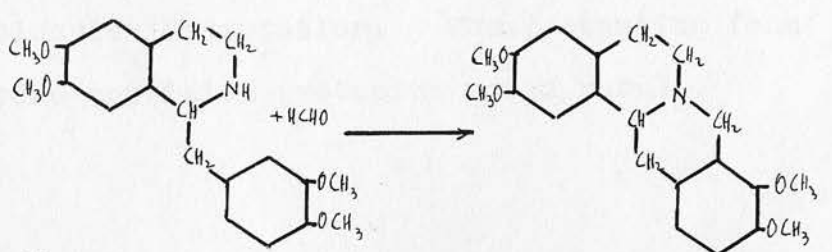
From the laudanosine skeleton, from its partly or wholly demethylated formula, all other more complex isoquinoline alkaloids can be derived (naturally not included pellot alkaloids and hydro-hydrastinine which was recently obtained from a natural source (3)).

The existence of laudanosine proves the presence of formaldehyde or other methylating agents in the plant tissue, by methylating an unknown "proto-alkaloid" laudenosine is obtained; from the same proto-alkaloid papaverine may be obtained by oxidation:



Papaverine Laudanosine

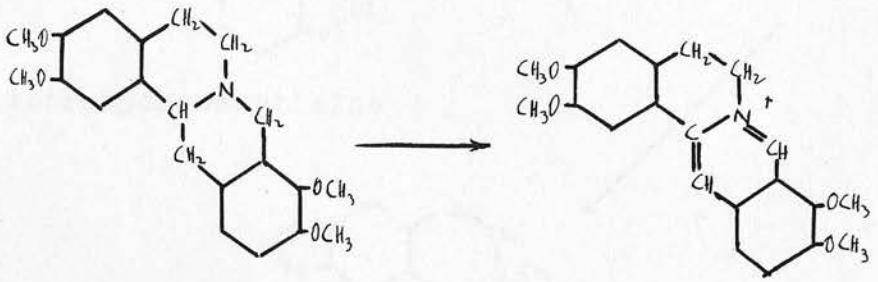
In the <u>berberine group</u> ring closure between nitrogen and the lower benzene ring is effected by means of an additional carbon atom which may be derived from formaldehyde:



Tetramethylether of proto-alkaloid

Tetrahydro-palmatine (corydaline group)

A similar oxidation as the one being responsible for the formation of papaverine can occur in this group, giving rise to berberine:

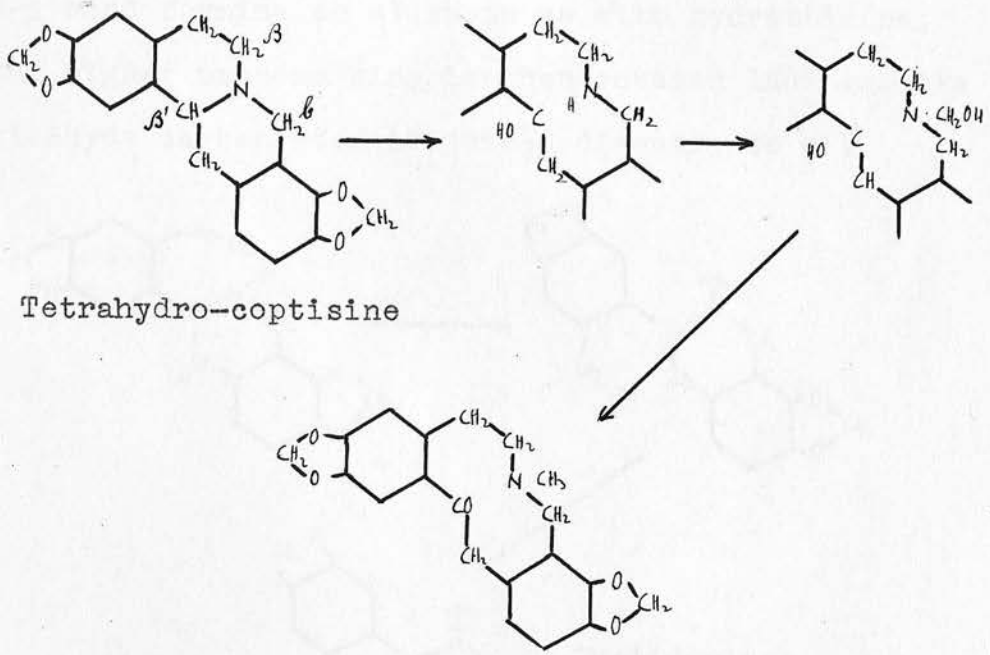


Tetrahydropalmatine or tetrahydroberberine

Berberine type

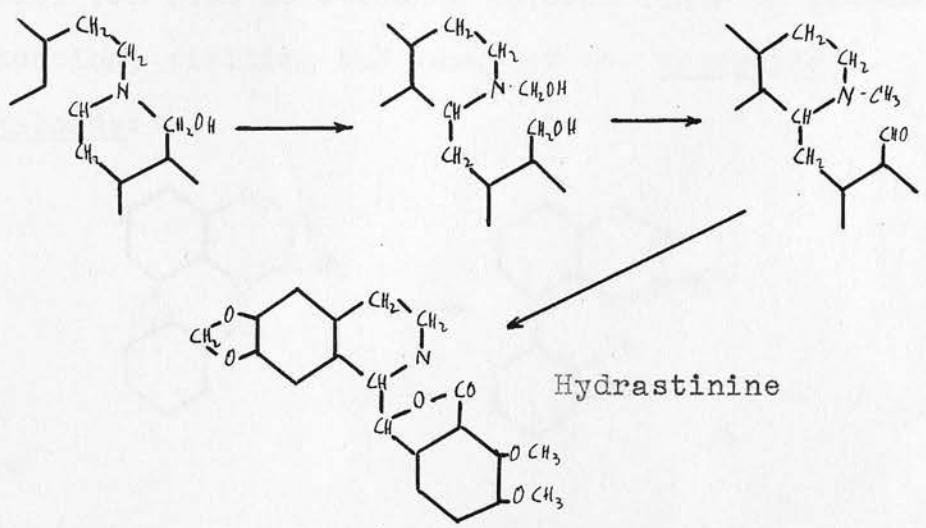
The nitrogen atom in tetrahydroberberine is attached to three different carbon atoms β, β' and C.; according to the theory of von Bruchhausen and Bersch (4), three further types of alkaloids can be derived by rupture of these attachments.

Protopine type. By addition of water the N-β' bond is opened; the resulting secondary base adds formaldehyde and water is again eliminated by an intramolecular dismutation. Thus, starting from tetrahydro coptisine protopine would result.



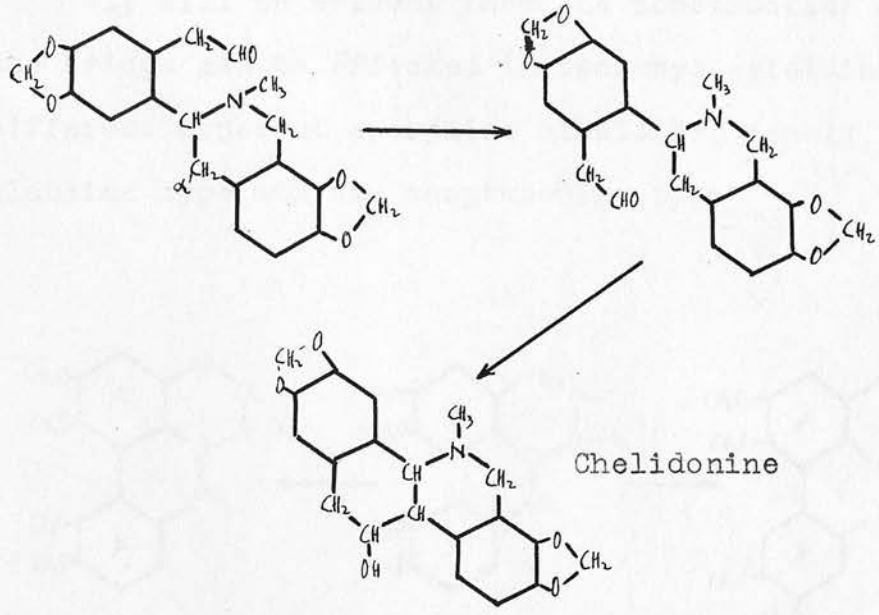
Tetrahydro-coptisine

The <u>hydrastinine-narcotine type</u> arises in similar fashion by the break between N and C. By subsequent oxidation a lactone results:



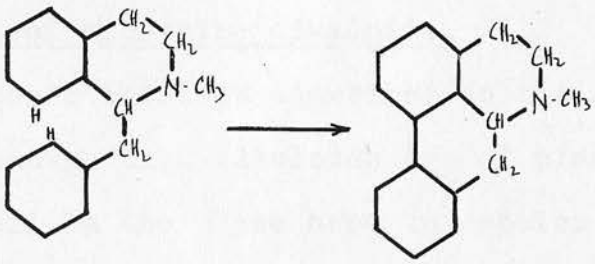
Hydrastinine

The chelidonine type arises by the loosening of the N-β bond forming an aldehyde as with hydrastinine; the higher benzene ring is then rotated 180° and the aldehyde carbon atom is joined directly to α'.



Chelidonine

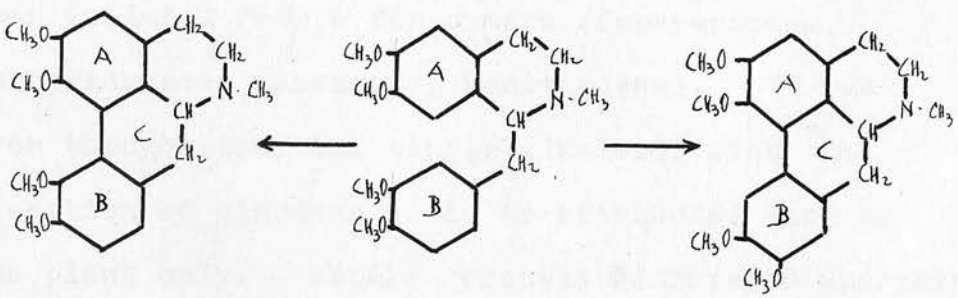
Finally starting from laudanosine the two benzene nuclei can also be attached to each other by simple oxidation, yielding the group of the aporphine alkaloids;



Under/

Under aporphine alkaloids or phenanthri-pyridine alkaloids we therefore understand a complex of a dihydro-phenanthrene ring system condensed with a partially reduced pyridine nucleus.

It will be evident that the construction of the bridge can be effected in two ways, yielding two different types of aporphine alkaloids, namely, the glaucine type and the corytuberine type:



Corytuberine type Glaucine type

2. Source of aporphine alkaloids.

Organic chemists sometimes do not realise clearly enough that alkaloids are of plant origin. It may well be the place here to mention a few words about/

about the distribution of the different bases. It is a fact that the same alkaloid usually occurs in one plant only or in a few plants nearly related to each other. The only exceptions from this rule are simple alkaloids; harman has been isolated from plants belonging to quite different natural orders (5, 6), but we may safely say that highly complex bases like strychnine occur in Strychnos species and will never be found in Papaveraceae for instance. Aporphine alkaloids, being rather complex, have only been isolated from a few orders (Papaveraceae, Berberidaceae, Lauraceae, Monimiaceae). It was even thought that the single alkaloids with the exception of glaucine could be attributed each to one plant only. Manske recently discovered aporphine bases in Fumariaceae which were thought earlier to occur only in Corydalis (7).

It may be worth while to give some information as to the distribution of these plant bases in nature:-

Aporphine is purely synthetic (8), apomorphine is obtained by heating morphine with concentrated hydrochloric acid in a sealed tube (9); by doing the same with thebaine morphothebaine is obtained(10).

Glaucine/

Glaucine is an alkaloid widely distributed; isolated by Probst from Glaucium luteum (11), and by Gadamer from Corydalis cava (12). Glaucine is dextro-rotatory ($[\alpha]_D$ = +113.3°); Go (13) isolated l-glaucine ($[\alpha]_D$ = -114.7°) from a Korean Corydalis. Manske recently found glaucine in a Dicentra species (14).

Dicentrine was isolated from several Dicentra species (15): D. formosa, spectabilis, pusilla.

Boldine: only isolated from the South American shrub Pneumus boldus, Boldea fragans (Monimiaceae) (16).

N-methyl-laurotetanine has recently been isolated by Späth and Suominen from crude laurotetanine (17). Working with an eight years old bark I have not succeeded in obtaining this base. Its existence was already strongly suspected by Barger and Silberschmidt (18).

Laurotetanine seems to be widely distributed; it was isolated by Greshoff from Litsea chrysocoma (19), by Gorter from L. cubeba and L. sebifera (20), by Filippo from L. citrata (21). About sixty species of Litsea have not yet been investigated according to Chopra's "Indigenous Plants of India" (22). Dr. Krishna/

Krishna of the Forest Research Institute of Dehra-Dun has recently isolated a new alkaloid from Litsea zeylanica. Actinodaphnine was isolated by Krishna and Ghose from Actinodaphne hookeri (23).

Corytuberine, corydine and iso-corydine were mainly isolated from Corydalis bulbs (24). For their isolation Gadamer and Ziegenbein have worked out a very detailed scheme (25). Corydine and iso-corydine have been isolated quite recently from Dicentra canadensis (26).

Bulbocapnine was isolated from Corydalis cava by Gadamer (27), quite recently by Manske from Dicentra canadensis (28).

Laurepukine isolated by Girardet from Laurelia pukatea (29).

Pukateine and laureline were isolated by Aston from Laurelia pukatea (30).

Domesticine and iso-domesticine were isolated by Kitasato from Nandina domestica (31). These two alkaloids are the only two known aporphine bases from a member of N.O. Berberidaceae.

Iso-thebaine was isolated by Gadamer and Klee (32) from withered leaves of Papaver orientale, the alkaloid/

alkaloid seems to be present in no other plant. Extracting green leaves Gadamer only obtained thebaine. Whether iso-thebaine originates from thebaine is unknown.

3. Some historical details on the research in the aporphine series.

In earlier years the most important work on aporphine alkaloids has been done by Gadamer. Gadamer introduced the name aporphine for the whole group and he also synthesised the simplest aporphine base (8). The constitution of apomorphine has mainly been worked out by Pschorr (33). In recent years Späth has done a good deal of work in the aporphine series.

Glaucine was the first alkaloid in this group to be synthesised by Pschorr (34) and Gadamer (35); in 1925 Perkin synthesised dicentrine in connection with his work on berberine and cryptopine (36).

In 1928 and 1929 a large number of aporphine alkaloids were synthesised simultaneously by Späth in Vienna and by Haworth and Gulland in Oxford. In more recent years some work on aporphine alkaloids has been done in the Medical Chemistry Department of Edinburgh/

Edinburgh University.

To-day the group of the aporphine alkaloids is probably one of the best known in alkaloid chemistry, but there are still a few problems to be solved.

4. Constitutional work.

Below is given a complete list of the nineteen known aporphine alkaloids as far as the constitution is known to-day. The author usually divides the aporphine alkaloids into different groups:

(1) Artificial and synthetic alkaloids (aporphine, apomorphine, etc.)

(2) Glaucine type.

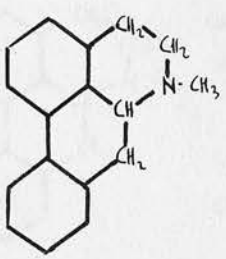
(3) Corytuberine type.

(4) Pukateine type.

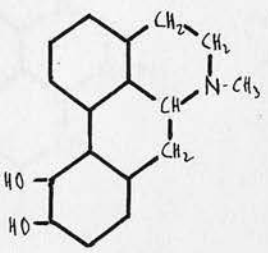
(5) Domesticine type.

(6) Isothebaine.

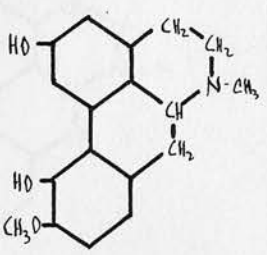
(1) Artificial alkaloids:



Aporphine



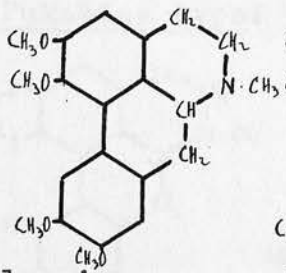
Apomorphine
$[\alpha]_D$ = -



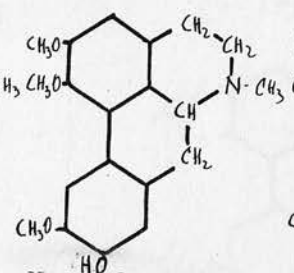
Morphothebaine
$[\alpha]_D$ = -

(2) Glaucine type:

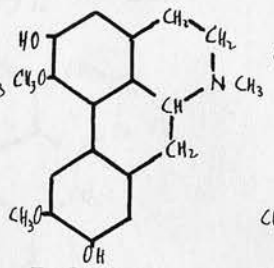
(a) tertiary bases:



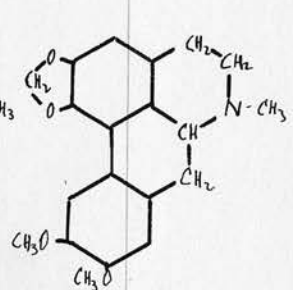
Glaucine
$[\alpha]_D$= +113.3°



N-methyl-laurotetanine: $[\alpha]_D$ = +

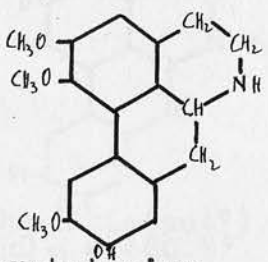


Boldine
$[\alpha]_D$ = +115°

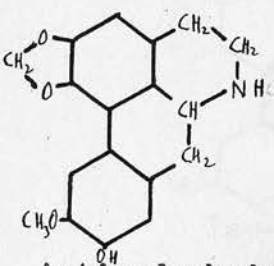


Dicentrine
$[\alpha]_D$ = 62.1°

(b) Secondary bases:

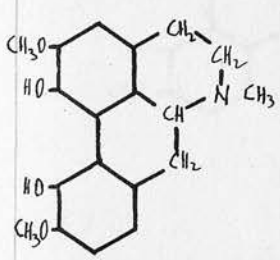


Laurotetanine
$[\alpha]_D$ = +98.5°

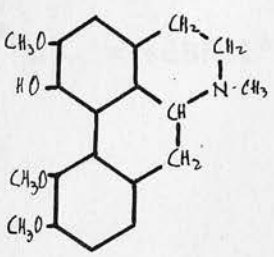


Actinodaphnine
$[\alpha]_D$ = +32.8°

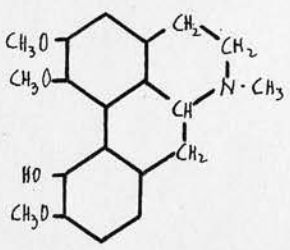
(3) Corytuberine type:



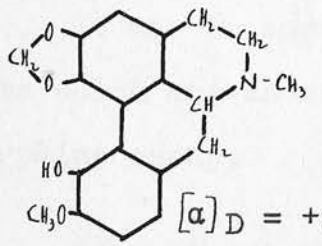
Corytuberine
$[\alpha]_D$ = +282.6°



Corydine
$[\alpha]_D$ = +204°

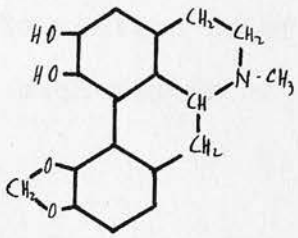


Isocorydine
$[a]_D$ = +195°



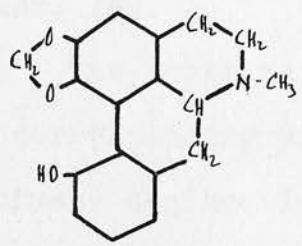
$[\alpha]_D$ = +237.1°

Bulbocapnine

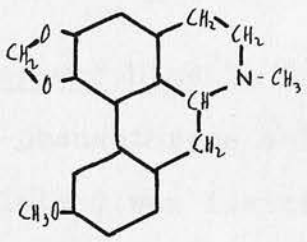


Laurepukine
$[\alpha]_D$ = -222°

(4) Pukateine type:

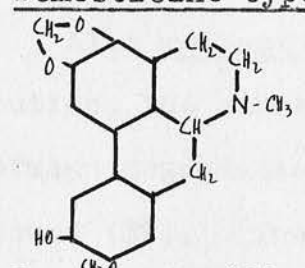


Pukateine
$[\alpha]_D$ = -220°

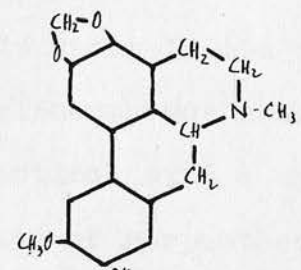


Laureline
$[\alpha]_D$ = -98.5°

(5) Domesticine type:(?)

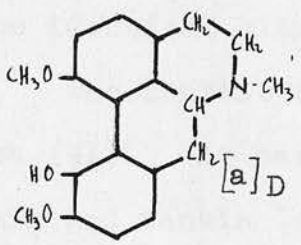


Domesticine(?)
$[\alpha]_D$ = +60.5°



Iso-domesticine(?)
$[\alpha]_D$ = ?

(6) Isothebaine.



$[a]_D$ = +285.1°

It may be advisable to mention briefly the facts which are known about each member of the aporphine group.

Aporphine is purely synthetic. It has been synthesised as already mentioned by Gadamer and co-workers (8).

The constitution of apomorphine is fully known, the corresponding dimethoxy-phenanthrene obtained by a Hofmann degradation (see later) was identical with a synthetic product (37) and apomorphine-dimethyl-ether has been synthesised by Späth and Hromatka (38).

Also morphothebaine is known in its constitution, the substituted phenanthrene obtained by a Hofmann degradation is identical with a synthetic compound (39). The synthesis of morphothebaine-methyl ether was effected by Gulland and Haworth(40).

Glaucine was synthesised by Gadamer and found to be identical with the natural product (35).

The constitution of dicentrine is fully known (41). It has been synthesised by Haworth, Perkin and Rankin (42).

The constitution of boldine forms part of this thesis; by methylating boldine, Warnat obtained glaucine (43). Späth and Tharrer synthesised the substituted/

substituted phenanthrene obtained by a Hofmann degradation (44); simultaneously r/diethyl-boldine was synthesised (45).

The constitution of N-methyl-laurotetanine is fully proved by a Hofmann degradation (17); also the constitution of laurotetanine is a part of this thesis. By methylating laurotetanine glaucine was obtained (18, 46). The full constitution was proved by Barger and co-workers (47).

Actinodaphnine is fully known apart from a slight doubt as to the respective positions of the methoxyl and the phenolic hydroxyl group (48). The elucidation of its structure forms the third part of this thesis.

The elucidation of the corytuberine structure is complete. Corytuberine-dimethylether has been synthesised by Gulland and Haworth (49) and by Späth and Hromatka (50). Späth and Berger have shown the respective positions of the substituents (51).

Corydine has been synthesised from bulbocapnine by Späth (51). The constitution of isocorydine has been definitely proved by Späth (51).

The constitution of bulbocapnine is fully known by oxidative degradation (52) and by Gulland and/

and Haworth's (53) and Späth and Hromatka's (54) synthesis of its methylation product.

The constitution of laurepukine is not known yet; Girardet accepts the given constitution as the correct one.

Pukateine and laureline: The constitution of both bases is fully known. Barger and Girardet's work made the proposed formulation highly probable (55); their views were later confirmed by the synthesis of pukateine-methylether (56) and laureline (57).

The constitutions of domesticine and iso-domesticine are not confirmed yet. Absorption spectra and some oxidation products render the given formula possible (31).

The constitution of isothebaine is not proved yet. A Hofmann degradation yielded a product which might possibly be identical with a synthesised compound (58). An attempt to synthesise isothebain-methylether by Callow, Gulland and Haworth failed (59).

(5)/

(5) Four general points on aporphine alkaloids.

(a) Rotation.

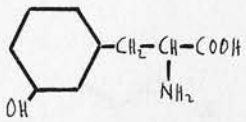
All aporphine alkaloids are optically active owing to the one asymmetric carbon atom; they are all dextro rotatory with the exception of apomorphine and morphothebaine. Also the three pukatea alkaloids are laevo rotatory.

(b) Alkaloids of the glaucine type melt at a higher temperature than those of the corytuberine type. Alkaloids with methylenedioxy groups melt at a higher temperature than those with only methoxyl groups.

(c) If there are hydroxyl and methoxyl groups in ring B, the hydroxyl group is always in positions 2 or 4 and the methoxyl group is in 3- position. Späth and Strauhal first pointed out this rule saying that derivatives of isovanillin occur more frequently in nature than those of vanillin (46).

(d) For all aporphine bases we can give a scheme according to which they are built up from two molecules of an amino acid (tyrosine or dioxyphenyl-alanine), the only exception being pukateine which in/

in its ring B must be derived from an amino acid which has not yet been found in nature: m-tyrosine (60).



(6) Degradation of aporphine alkaloids.

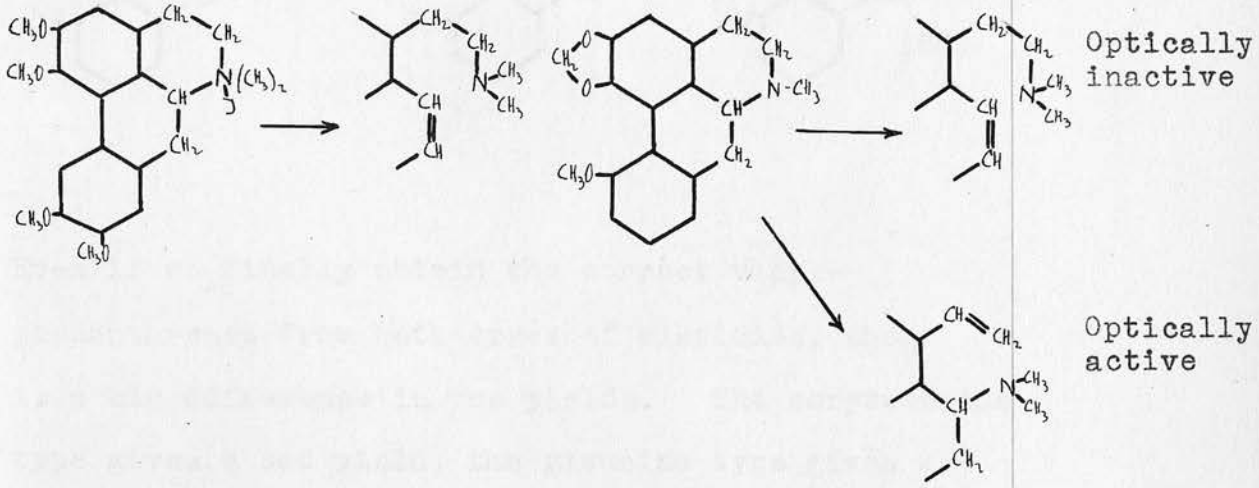
For most of the degradations one uses the fully alkylated compounds. Alkylation can be effected by dimethyl sulphate, diazomethane or diazoethane. Mostly the bases react readily; apomorphine (61, 62), laurepukine (29) and corytuberine (63) react very slowly; methylation with diazomethane in statu nascendi in amyl ether suspension is quite effective (63, 29).

(a) Hofmann degradation.

The step by step removal of the N atom and subsequent elimination of the two carbon atoms is called Hofmann degradation. By this method substituted phenanthrenes are obtained from aporphine bases which then may be synthesised.

In the first step the glaucine type yields an optically inactive, crystalline tertiary methine base, the/

the corytuberine type yields a mixture of optically active and inactive methine bases which are both oily:



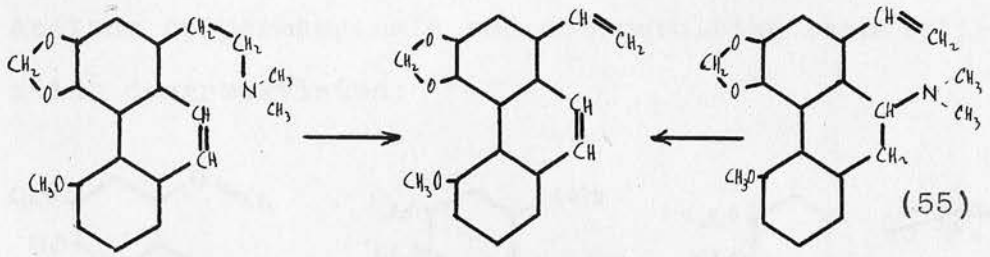
I. Glaucine: Barger-Silberschmidt (18).
Boldine : Warnat (43)
Laureline: Barger-Girardet (55)
Dicentrine: Manske (65)
Actinodaphnine: Ghose-Krishna-Schlittler (48)

II. Pukateine: Barger-Girardet (55)
Bulbocapnine: Gadamer (64)
Isothebaine: Klee (58)
Apomorphine: Pschorr, Gadamer (66)
Corytuberin: Gadamer (67)

The second step of the degradation (removal of N as trimethylamine) yields the same vinyl-

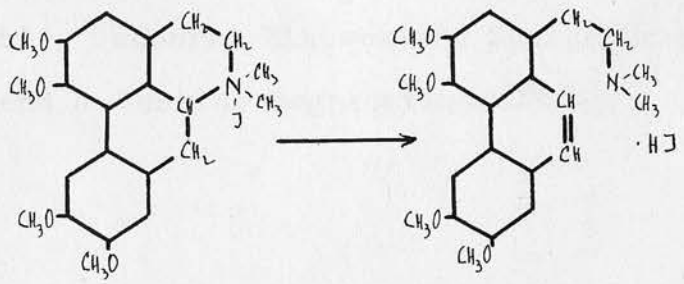
phenanthrene/

phenanthrene from both active and inactive methine.

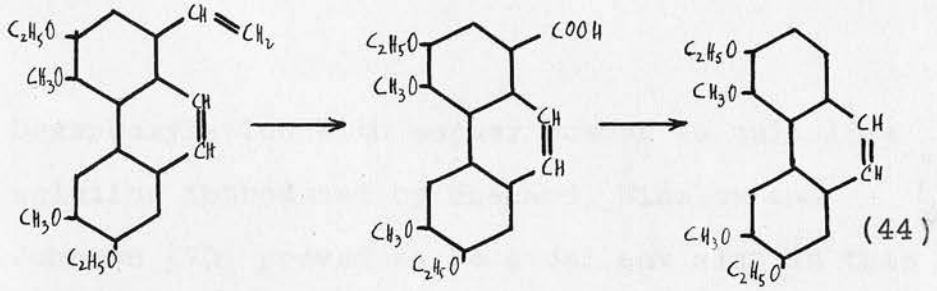


(55)

Even if we finally obtain the correct vinyl-phenanthrenes from both types of alkaloids, there is a big difference in the yields. The corytuberine type gives a bad yield, the glaucine type gives a very good yield. It has been possible to effect a Hofmann degradation with 40 mgm. of an aporphine base of the glaucine type. The author remembers a laboratory experiment when glaucine methiodide was heated almost to its melting point in high vacuum. Within half a minute glaucine methiodide passed almost quantitatively into the methine hydriodide.

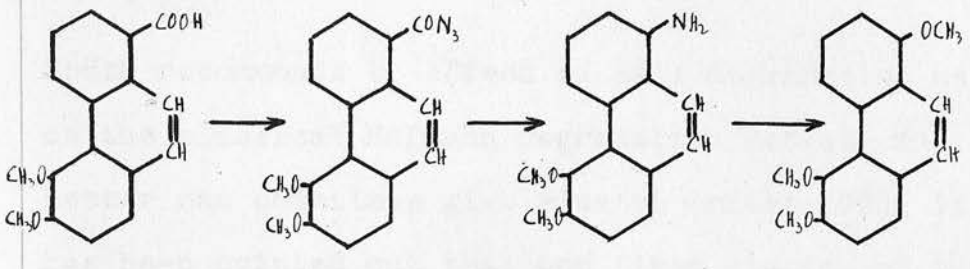


The vinyl-phenanthrenes then are oxidised in acetone by permanganate and the resulting carboxylic acids decarboxylated:



(44)

The oxidation usually gives a yield of about 50%. Considerable quantities of a neutral glycol are formed as well. Decarboxylation is sometimes very difficult or even impossible (18); often it may be effected by heating the carboxylic acid to 240° and higher (55) or by heating with glacial acetic acid in a sealed tube or by heating with glycerol (compare Klee [68]). If there is much material available, Pschorr, Einbeck and Spangenberg recommend a Curtius degradation. (69).

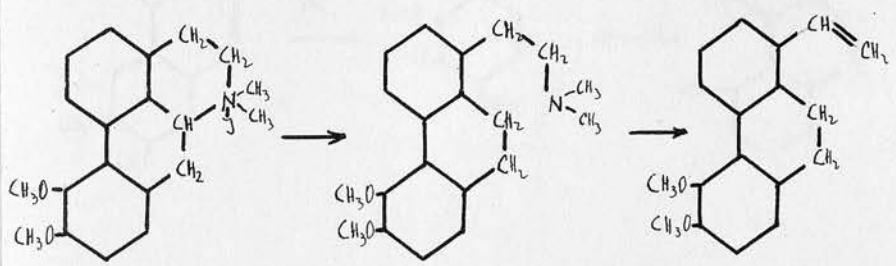


Decarboxylation with copper powder in quinoline solution introduced by Shepard, Winslow and Johnson (70) proved to be excellent also in this group.

A large amount of such substituted phenanthrenes have been synthesised and compared with the natural degradation products.

(b) Emde degradations (71)

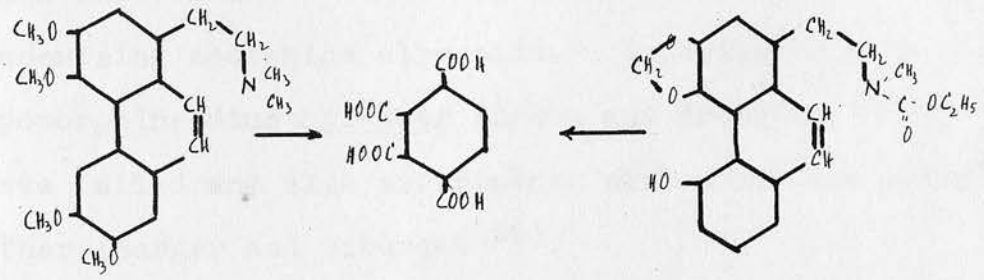
Emde degradations have been effected on apomorphine (72), bulbocapnine (52) and laurotetanine (46). This kind of degradation is not commonly employed as it gives rise to dihydrophenanthrenes which are not easily synthesised (72).



Späth recommends to effect an Emde degradation as well as the classical Hofmann degradation because the latter can sometimes give rise to errors (73). It has been pointed out that the first opening of the nitrogen ring by an Emde degradation also in the corytuberine type proceeds in one direction only.

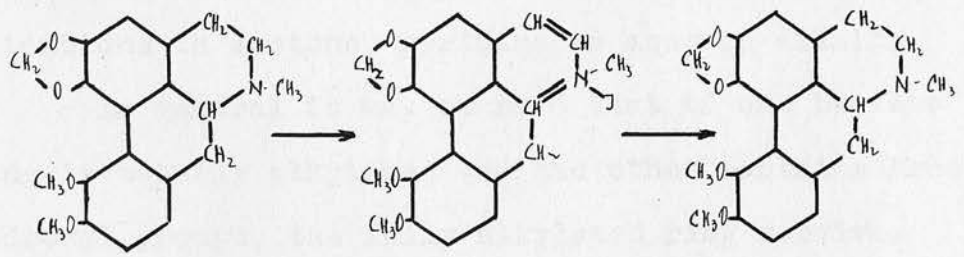
(7) Oxidations.

(i) Nitric acid. Oxidation of aporphine alkaloids with concentrated nitric acid does not yield any well defined products. Warnat was the first to show (43) that mellophanic acid is obtained if an aporphine alkaloid in which the N-ring has previously been opened is oxidised. This may be done by a Hofmann degradation (43, 48), by an Emde degradation (46) or by means of ethylchloro-carbonate (55), which reagent opens the N-ring especially easily (74).



The formation of mellophanic acid is conclusive for the aporphine structure.

(ii) Iodine: Oxidations with iodine are only of limited use with aporphines. Gadamer and Kuntze (75) oxidised bulbocapnine methyl ether and corydine with iodine to the optically inactive quaternary dehydro-bulbocapnine methyl ether hydriodide; by reduction he obtained optically inactive bulbocapnine methyl ether.



This oxidation and reduction is valuable for racemising aporphine alkaloids. Experiments with apomorphine-dimethylether (Späth and Hromøtka (38)) have failed and also experiments with pukateine methyl ether (Barger and Girardet(55).

(iii)

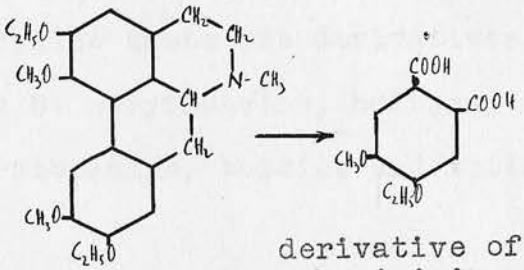
(iii) Mercuric acetate: Oxidation with mercuric acetate has rendered valuable services in other groups of alkaloids. Gadamer (76) and Girardet (55) have however failed to obtain definite results. Professor Robinson has been able to oxidise dibenzyl-apomorphine to the optically inactive dehydro compound with mercuric acetate and subsequently to reduce this compound again (77).

(iv) Permanganate: Oxidations in strongly acid solution are usually unsuccessful, better are oxidations in acetone, pyridine or aqueous alkali.

In general it may be said that if one benzene ring is totally alkylated and the other contains free hydroxyl groups, the fully alkylated ring survives oxidation, the other being totally destroyed. If the base is fully alkylated and methoxyl as well as methylene-dioxy groups are present, the benzene nucleus with the methylene-dioxy group is always destroyed, being less stable. The oxidation products are mostly substituted phthalic or hemimellitic acids. If the alkaloid contains hydroxyl as well as methoxyl groups, the first are usually ethylated by means/

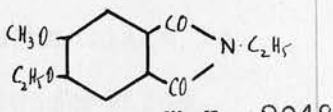
means of diazoethane thus marking them from the beginning as being originally free hydroxyl groups.

(α) Oxidation products of ring B: Alkaloids of the glaucine type (glaucine, laurotetanine, boldine, actinodaphnine) yield on oxidation substituted m-hemipinic acids which are symmetrical. A conclusion concerning the arrangement of the different substituents is therefore impossible.

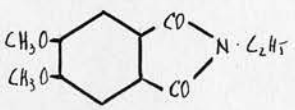


(45)

derivative of m-hemipinic acid

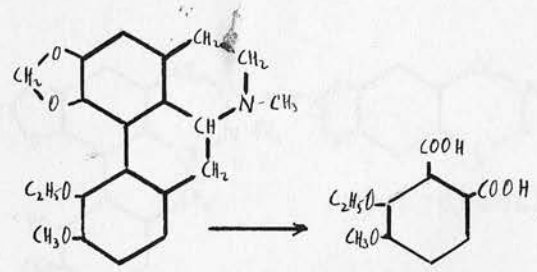


m.p. 204°



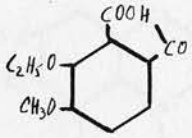
m.p. 232°

The corytuberine type yields the unsymmetrical hemipinic acid which allows a conclusion to be drawn:

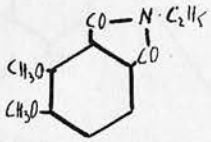


(52); similarly (51).

Derivative of hemipinic acid



m.p. 84°



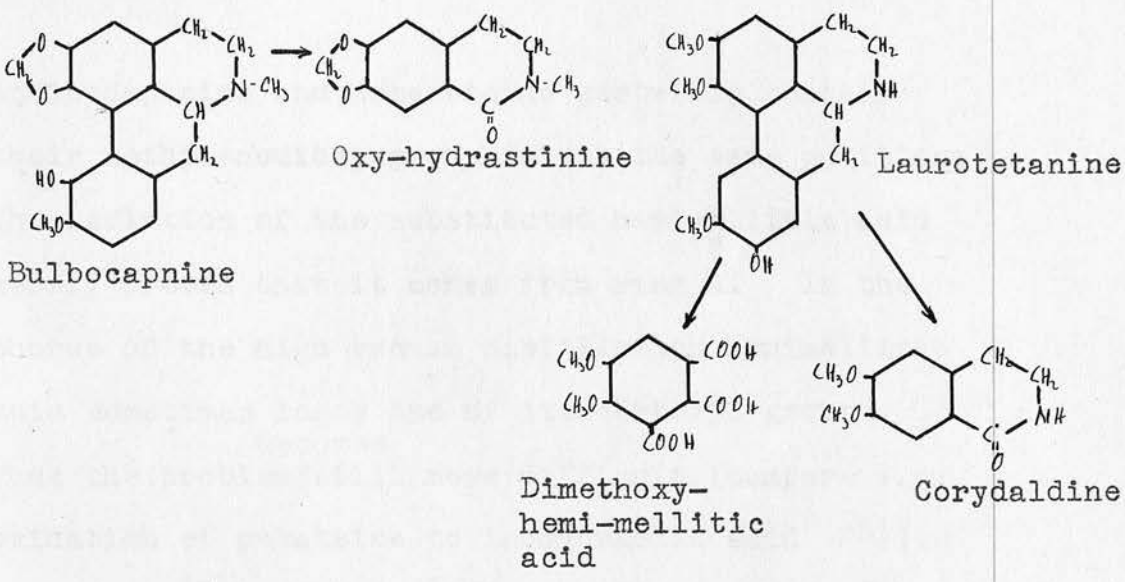
The substituted hemipinic acids are usually identified as ethylimides, the differences in melting points is such as not to allow any errors.

As already mentioned all hitherto known aporphine bases are derivatives of isovanillin in ring B: corytuberine, bulbocapnine, isocorydine, laurotetanine, boldine and actinodaphnine.

(β) Oxidation products of ring A.

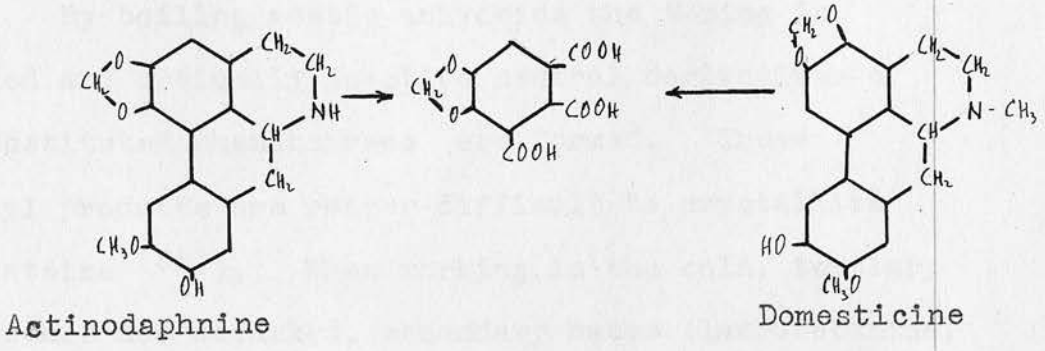
It is extremely rare that mild oxidation can be directed in such a way as to obtain degradation products which are at first sight conclusive for the arrangement of all substituents in ring A.

Späth, Holter and Posega succeeded in obtaining oxyhydrastinineby oxidation of bulbocapnine (52).



Usually only derivatives of hemimellitic acids are obtained. Oxidising laurotetanine Späth and Strauhal (46) did not succeed in isolating corydaldine but merely obtained dimethoxy-hemimellitic acid (78).

In the same way by either oxidising actinodaphnine (48) or domesticine (31) methylenedioxy-hemimellitic acid is obtained (79).



Actinodaphnine and domesticine certainly contain their methylenedioxy group not in the same position; the isolation of the substituted hemimellitic acid merely proves that it comes from ring A. In the course of the high vacuum distillation hemimellitic acid sometimes loses one of its carboxyl groups. Thus the problem becomes still more difficult (compare e.g. oxidation of pukateine to isohydrastic acid (55)).

Oxidation experiments are certainly very valuable but in 90% of the cases they do not give conclusive evidence and only a synthesis can give final proof for the constitution of an alkaloid.

(8) Some other general reactions of aporphine alkaloids:

(a) Reaction with acetic anhydride

By boiling acetic anhydride the N-ring is opened and optically inactive neutral derivatives of a substituted phenanthrene are formed. These acetyl products are rather difficult to crystallise (pukateine (55)). When working in the cold, tertiary bases are not attacked, secondary bases (laurotetanine, actinodaphnine/

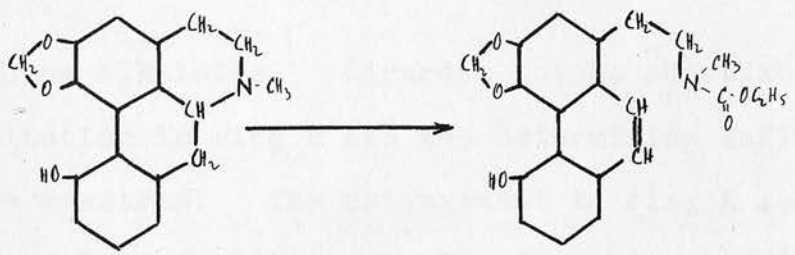
actinodaphnine) are acetylated. This serves e.g. for the separation of the crude alkaloids of the Litsea bark (46, 17).

b. Reaction with benzoyl chloride.

Boiling benzoyl chloride opens the N-ring as well. An optically inactive neutral substance results which is sometimes crystalline. Späth having at his disposal too little synthetic apomorphine-dimethylether for resolution, prepared its benzoyl product and compared it with the corresponding benzoyl product of natural origin (38). Also for identification of synthetic laurotetanine derivatives the benzoyl product was used (47) (Barger, Eisenbrand, Eisenbrand and Schlittler).

c. Reaction with ethylchlorocarbonate.

It was Gadamer and Knoch who showed that the N-ring of tertiary aporphines is extremely easily opened, even at 0°, by ethylchlorocarbonate (74). Fission always occurs in one way only contrary to the Hofmann degradation. The reaction products are optically inactive and neutral; they can be recrystallised fairly easily (45, 47, 49, 80).



This type of optically inactive compound is useful for comparison of natural and synthetic products. Gulland and Haworth used such a carbethoxy-derivative in their synthesis of corytuberine-dimethylether (49). Recently it has been used in the synthesis of boldine and its isomer (45) and for derivatives of laurotetanine (47). The great advantage is that one can work at 0°, no resinification takes place as is the case when working with boiling benzoyl-chloride.

The carbethoxy-group cannot be removed any more from the N; Osada claims to be able to do so by heating with N/2 KOH to 150-160°; this is the only case known in the aporphine group (80).

(9) Absorption spectra.

Steiner (81) and especially Kitasato (31) and Girardet (82) have studied the absorption spectra of aporphine/

aporphine alkaloids. Girardet points out that the substitution in ring B has the determining influence on the spectrum. The arrangement in ring A seems to be of less importance. Based on his experience he has proposed the present formula for laurepukine (29). Definite conclusions should not be drawn from such spectra but in a well known field, such as in the aporphine group, the study of those spectra is of considerable value.

(10) Synthetic work on aporphine alkaloids.

Robinson (83) has demonstrated that the isoquinoline alkaloids are probably built up in the plant cell from a hydroaromatic aldehyde and a hydroaromatic amine by a series of complex reactions. These reactions are influenced by stereochemical relations of the hydroaromatic substances, by the rapidity with which they lose water, by the concentration of formaldehyde present, by the presence or absence of enzymes or other catalysts - all these factors account for the wide variation of the isoquinoline group.

The organic chemist is naturally unable to work under similar conditions; he starts with purely/

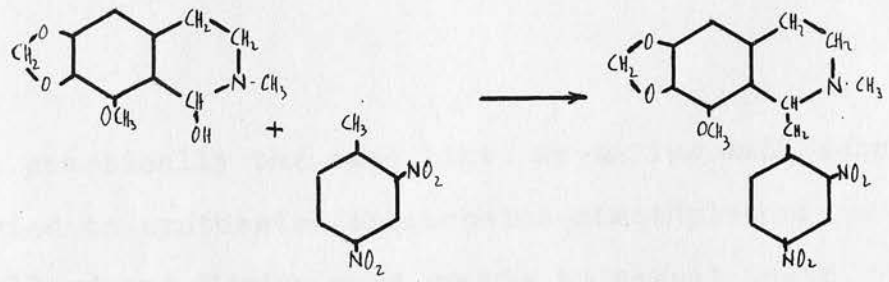
purely aromatic substances and builds up an aporphine skeleton. Incidentally the way of synthesis may be called somewhat similar to the way used in nature.

There are two fundamentally different ways for the synthesis, the last step of both syntheses being a Pschorr phenanthrene ring-closure:

(i) one starts with an already preformed isoquinoline nucleus,

(ii) one starts with a substance which only in the course of the reactions is converted into an isoquinoline complex, the nitro- group being introduced from the beginning or after isoquinoline ring closure (compare e.g. (42)).

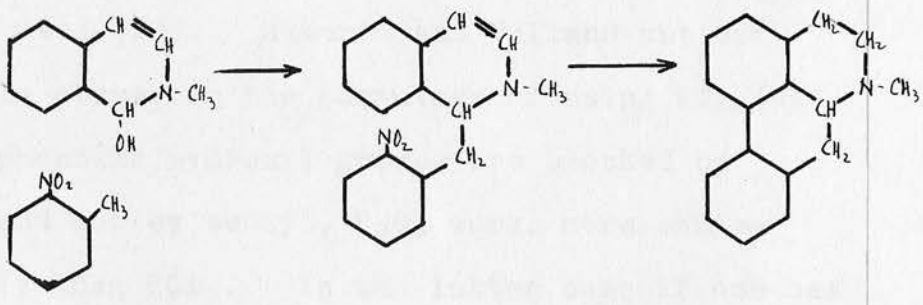
Method (i). is only of limited use. Hope and Robinson found that the pseudo base of cotarnine condenses with derivatives of o-nitrotoluene to the corresponding o-nitro-benzyl-isoquinoline (84).



But/

But hydrastinine does not condense with mononitro-toluene, thus ruling out any simple synthesis of aporphine alkaloids with a methylene-dioxy group in ring A (85). This way was used for the synthesis of isoapomorphine-dimethylether (86).

Fifteen years had elapsed between the two publications and meantime this field had engaged the attention of other investigators. It was Gadamer, Oberlin and Schöler who in 1924 synthesised aporphine in a similar way (8).



On practically the same lines Avenarius and Pschorr tried to synthesise apomorphine-dimethylether (87). Gulland and Virden were unable to repeat their synthesis (88).

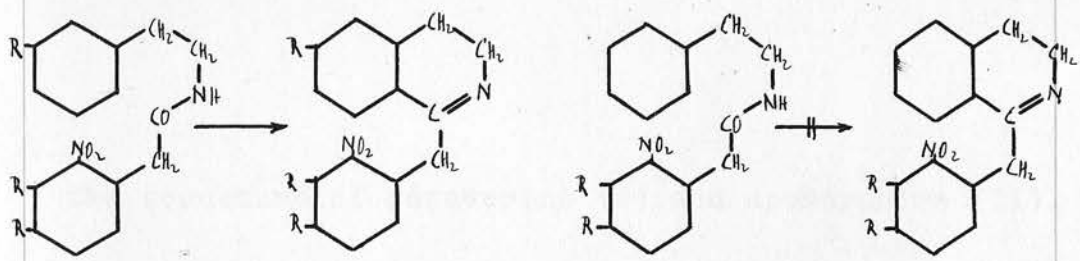
Method (ii) /

Method (ii).

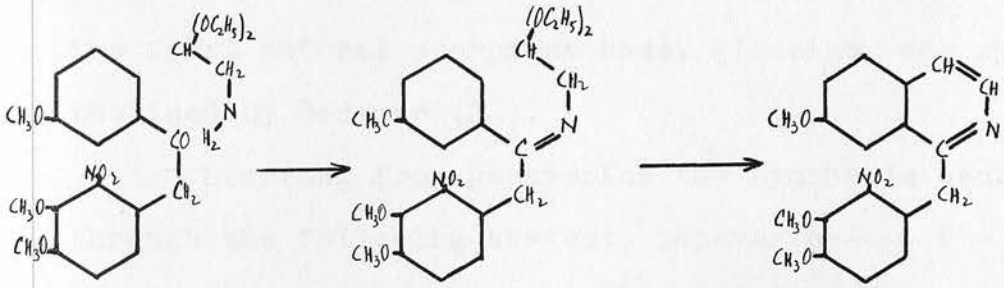
This is the way originally initiated by Pictet. A ring closure of a substituted acid amide to an isoquinoline derivative by the Bischler-Napieralski method (89). If the benzyl group then is suitably substituted by a nitro group or nitrated after formation of the isoquinoline complex, a second ring closure according to Pschorr's method leads to an aporphine base.

As condensing agents for the formation of the iso-quinoline ring P_2O_5, PCl_5, $POCl_3$ and concentrated HCl are used (90). Haworth and Gulland put considerable stress on the advantage of using PCl_5 (91). If the phenolic hydroxyl groups are blocked by methyl and not by benzyl, P_2O_5 works more satisfactorily than PCl_5. In the latter case if one has to work at low temperature naturally only PCl_5 can be used.

The ease of the isoquinoline ring closure depends very much on the presence of an activating substituent. If such a substituent is not present ring closure becomes difficult (92).



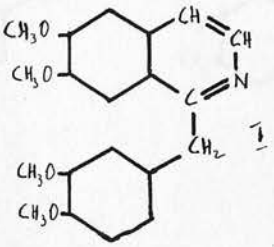
Isothebaine is a particularly difficult case, the methoxyl group being in meta and not in para position. A synthesis by Callow, Gulland and Haworth has failed (59). If isothebaine-methylether is ever going to be synthesised it will be by the Pomeranz-Fritsch synthesis starting from a substituted desoxy-benzoine (93) (but compare unsuccessful papaverine synthesis by Fritsch (94)).



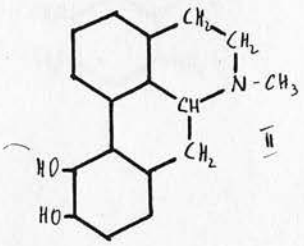
Follow usual way of synthesis

There is certainly a close resemblance between the/

the structure of papaverine (I) and apomorphine (II).



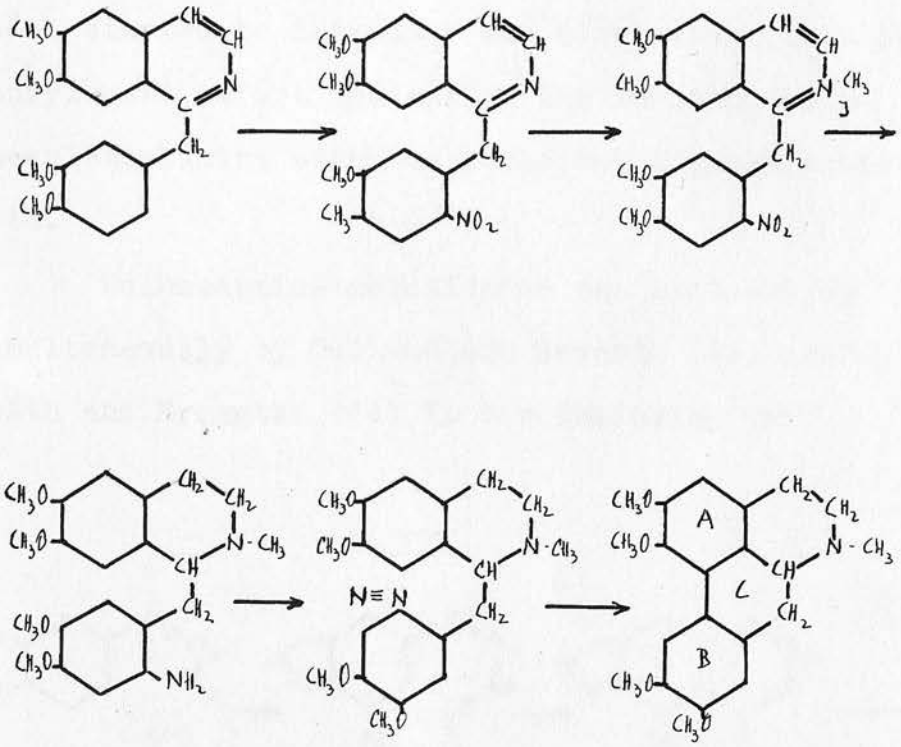
I



II

Pschorr who some time before had discovered his famous phenanthrene synthesis and was working on apomorphine considered it to be interesting to convert a papaverine derivative into a phenanthrene derivative. Pschorr was unable to isolate a well defined phenanthrene derivative (37); also he did not realise that he indicated the way by which later the first natural aporphine base, glaucine, was synthesised by Gadamer (35).

Starting from papaverine the synthesis went through the following stages: papaverine ⟶ 6'-nitropapaverine ⟶ 6'-nitropapaverine methiodide ⟶ 6'-aminolaudanosine ⟶ 6'-diazolaudanosine ⟶ glaucine.



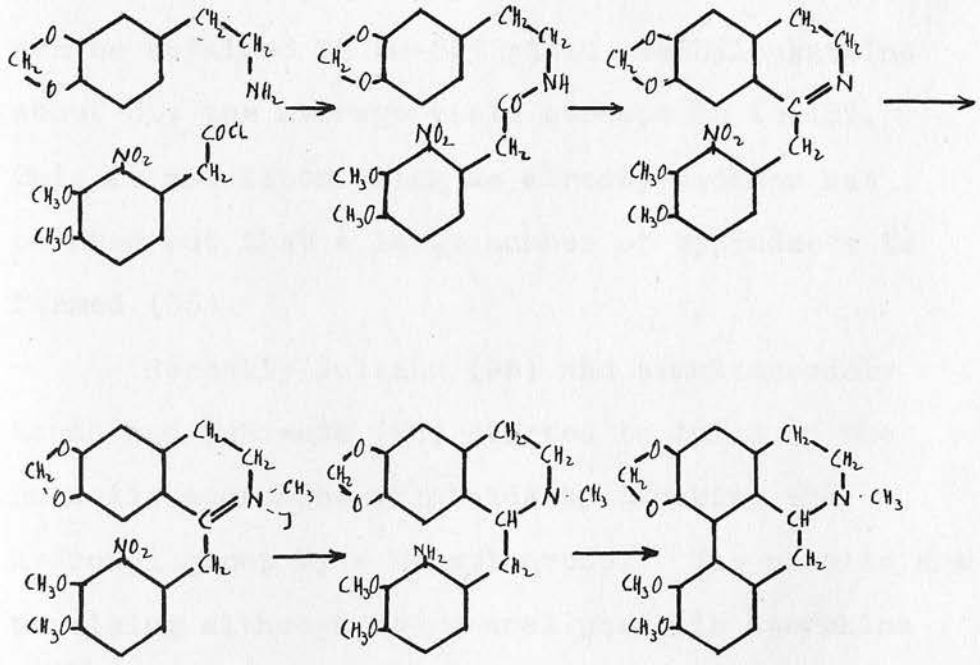
The nitro group in this case goes into the free p-position to the methoxyl group in ring B; a synthesis of the corytuberine type was not possible. Dicentrine was synthesised by Haworth, Perkin and Rankin on practically the same lines(42).

The synthesis of phenanthrene alkaloids only became general when Haworth and simultaneously

Späth/

Späth started to introduce the nitro group into the benzyl part before condensing the substituted β-phenylethylamine with the substituted phenylacetic acid.

Bulbocapnine methylether was synthesised simultaneously by Gulland and Haworth (53) and by Späth and Hromotka (54) in the following way:



In this way were synthesised the methyl ethers of bulbocapnine (53, 54), corytuberine (49, 50), apomorphine (38)(Späth-Hromotka), morphothebaine (40), and pukateine (56), further laureline (57), boldine-diethylether and one of its isomers (45) and the two possible O-N-diethyl-laurotetanines (47).

The yields of the different stages of the synthesis are usually quite satisfactory with the exception of the last one, the phenanthrene ring closure. There the yield often varies. Laureline can be obtained in 30-35% yield, methylpukateine about 5%; the average yield perhaps is 10-15%. This is not astonishing as already Gadamer has pointed out that a large number of byproducts is formed (35).

Recently Gulland (95) and simultaneously Kondo and Ishiwata (92) started to build up the phenolic aporphine alkaloids by blocking the hydroxyl group by a benzyl group. The results are promising although no natural phenolic aporphine has actually been synthesised. The method is not quite new, already in 1922 Späth and Röder have synthesised anhalamine by blocking its only hydroxyl by a benzyl group (96).

Optical/

Optical activity of synthetic aporphines.

Contrary to the corydaline group the resolution into the optical isomers is easily affected by means of l-and d-tartaric acid. After a few crystallisations of the tartrate from absolute alcohol, the salt and afterwards the free base show a correct rotation.

PART II.

On the Constitution of Laurotetanine, Boldine and Actinodaphnine.

(1) Example of extraction of an aporphine alkaloid.

Besides doing constitutional work, the author of this thesis has also extracted a number of alkaloids from plant material.

The search for N-methyl-laurotetanine strongly suspected to be present in Litsea bark by Barger and Silberschmidt (18) has been in vain. There is a possibility that N-methyl-laurotetanine is easily oxidised in the bark; working with an eight years old bark no trace could be detected. Späth and Suominen, working with fresher bark were able to isolate this base (17).

A good example for such an extraction from natural material is the preparation of the three pukatea alkaloids which I undertook along the lines given by Barger and Girardet (55). The details of the extraction sometimes were considerably modified. These extractions were done according to purely empirical experiments. After small scale experiments we/

we used zinc percolators about 5 ft. high, holding about 5 kilos of material each.

15 Kilos of finely ground laurelia bark divided over three percolators were percolated with ordinary ethyl alcohol containing about 0.5% of acetic acid for about ten days until there was no trace of a Mayer reaction (K_2HgI_4) in the percolator left. About 220 litres of alcohol resulted. This volume was evaporated in vacuo to about 15 litres which were put into the ice-chest, and in the course of a week a large amount of tar had separated. The pitch dark solution was afterwards slightly diluted with water and worked up in quantities of one litre approximately. Much sodium acetate was added and the total alkaloids were extracted with chloroform. The chloroform was extracted again with dilute H_2SO_4 which on standing deposited a mixture of much laurepukine and little laureline sulphate. The mother liquors were made alkaline by sodium carbonate and the alkaloids taken up into benzene; from that solution pukateine and very little laureline was removed by 10% acetic acid. The laureline in the acetic acid solution was precipitated as hydrobromide by potassium bromide, pukateine hydrobromide/

hydrobromide being rather soluble. Most of the laureline was still in the benzene and was removed from it by shaking with 2N. HCl. The hydrochloride crystallised from this solution as a red solid; it can easily be purified over the tartrate.

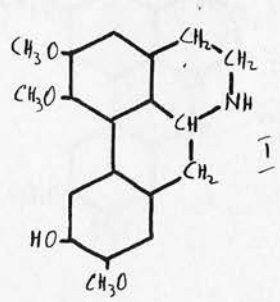
On the whole, aporphine alkaloids are very oxidisable and under any circumstances caustic alkalis must be avoided.

The halogen salts of the fully alkylated aporphine bases are soluble in chloroform. We often made use of this fact for the separation of aporphines from other alkaloids in synthetical as well as in experiments with natural products.

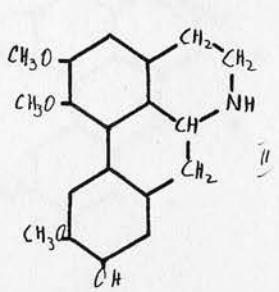
(2) The Constitution of Laurotetanine.

(A.) Theoretical part.

Barger and Silberschmidt (18) as well as Späth and Strauhal (46) attributed either of the two formulae I or II to laurotetanine, an alkaloid discovered in various Lauraceae by Greshoff (19).



I

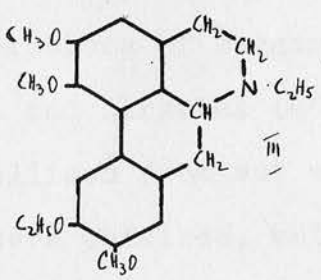


II

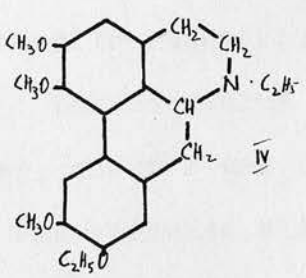
By methylating laurotetanine glaucine is obtained and not isoglaucine as Gorter (21) presumed. Therefore laurotetanine methylether is not identical with 2-3-6-7 or 3-4-6-7 tetramethoxy-aporphine which both were synthesised by Callow, Gulland and Haworth (97), the former having the constitution which Gorter proposed for isoglaucine.

Laurotetanine therefore was ethylated and afterwards several optically inactive products were prepared which were identical with synthetic material having the ethoxy group in 2- position. They were distinctly different from those having methoxyl group in 3- position so that now formula II must be attributed to the alkaloid laurotetanine.

The author's share in this research was only to extract laurotetanine from Litsea bark, to prepare the degradation products and also to prepare the corresponding degradation products of compounds III and IV synthesised by Dr and Mrs Eisenbrand of Berlin.



III



IV

As it was impossible to crystallise compounds III and IV, a Hofmann degradation on III, IV and the natural base was effected and trimethoxy-ethoxy-8-vinyl-phenanthrenes were obtained which melted without decomposition. The derivative of laurotetanine was identical with the one synthesised starting from isovanillin (IV) and showed a considerable depression in the melting point when mixed with the derivative of III. By the action of ethylchloro carbonate (74) and benzoyl chloride (38) on III, IV and the natural product further crystalline products for comparison were obtained and supplied further evidence for the correctness of our assumption.

B. Experimental Part.

(a) Extraction of the bark:

5 Kilos of Litsea bark were percolated with 40 litres of 70% ethyl alcohol (containing 0.5% of acetic acid); the alcohol was distilled off in vacuo and the residue treated according to prescriptions of Barger and Silberschmidt(18) and Späth and Strauhal (46). Laurotetanine was crystallised from wet ether, about 5 gm. of the base were obtained, which was coloured slightly yellow/

yellow, m.p. 125-130°.

For further identification laurotetanine-phenylthio-carbamide was prepared (21) which melted at 208° when recrystallised from alcohol.

(b) Ethylation of laurotetanine: By methylating laurotetanine with diazomethane, Späth and Strauhal obtained glaucine in a yield of 23%. Most of the base methylated at the phenolic hydroxyl only, the secondary nitrogen remains unchanged. By acting on laurotetanine with diazoethane Späth and Strauhal prepared ethyl laurotetanine. They suppose that the reaction product is a mixture of o-ethyl-laurotetanine and O-N-diethyl-laurotetanine. Nevertheless the yield of the latter compound is so extremely small that we had to seek for another way for its preparation.

Laurotetanine (0.4 gm.) was dissolved in absolute alcohol (4 c.c.) and a concentrated solution of diazoethane in ether (from 4 c.c. of N-ethyl-nitroso-urethane) was added. The solution was kept at room temperature for 16 hours. Phenolic and non-phenolic bases were separated by caustic soda, the latter were taken up into ether. By evaporating/

evaporating the ether a yellow oil (0.464 gm.) was obtained. The oil was dissolved in a few c.c. of acetone and left standing for 3-4 days with an excess of ethyl iodide. The crystals which had separated (0.32 gm.) were filtered, treated with NaOH, the mixture of secondary and tertiary bases were taken up into ether. The caustic mother liquors contained any quaternary base formed in the course of the reaction. After evaporating the ether a yellow oil (0.257 gm.) was obtained, freshly distilled acetic anhydride (2 c.c.) was added and the whole kept at room temperature for 7 hours. Then the mixture was cooled and water (15 c.c.) and so much concentrated HCl were added that the aqueous solution contained about 3% of HCl. The acetyl compound of the unchanged secondary compound was removed by extracting with much ether, caustic soda was then added and O-N-diethyl-laurotetanine taken up in ether. The tertiary base was extracted from ether again by shaking repeatedly with small amounts of 15% acetic acid solution. To this solution in acetic acid a concentrated solution of potassium iodide was added, the hydriodide being precipitated. Twide recrystallised from absolute alcohol it melted at/

at 210° with decomposition.

3.895 mgm. subst. 7.76 mgm. CO_2 + 2.160 mgm. H_2O

5.130 mgm. subst. 2.35 mgm. AgI

$C_{23}H_{30}O_4N.I$ calc. C = 54.01, H = 5.87, I = 24.86

found C = 54.34, H = 6.16, I = 24.36

The free base remained oily even after distillation in high vacuum; it was very soluble in all organic solvents, even in petrol ether.

(c) Hofmann degradation of O-N-diethyl-laurotetanine.

The hydriodide of O-N-diethyl-laurotetanine (0.1 gm.) was converted into the oily base, dissolved in a mixture of ether-acetone and excess of methyl iodide was added. The separated crystals were filtered on the following day and recrystallised from water. This methiodide (0.078 gm.) was dissolved in water (7.8 c.c.) and caustic soda (1 gm.) was added, the mixture being boiled under reflux for an hour. The oily tertiary base was extracted with ether, the ether evaporated, the base dissolved in a few drops of acetone and excess of methyl iodide was added. We thus obtained 0.055 gm. of the methiodide; it was dissolved in hot water (6 c.c.) and treated with freshly precipitated silver chloride, when we obtained/

obtained the corresponding methochloride. The aqueous solution of the methochloride was concentrated to a few c.c., solid caustic potash added and heated over the free flame until no more ethyldimethylamine was evolved. The highly concentrated solution was extracted with ether, the ether was distilled off, it left 0.043 mg. of ethoxy-trimethoxy-8-vinyl-phenanthrene. By recrystallising twice from alcohol 25 mgm. of pure product were obtained in small highly refractive plates, m.p. 143°. A mixed melting point with 2-3-5-6 tetramethoxy-8-vinyl-phenanthrene (from glaucine) which also melts at 142° showed a depression of 12°.

4.047 mg. subst. 11.12 mg. CO_2, 2.41 mg. H_2O

$C_{21}H_{22}O_4$ calc. C = 74.55, H = 6.51.

found C = 74.94, H = 6.59

0.005 gm. of above vinyl product were dissolved in acetone (1 c.c.) previously distilled over permanganate. Potassium permanganate (0.0078 gm.) dissolved in a few drops of acetone were added. The following day manganese dioxide was filtered off, well washed with water and washings and acetone united. The solution was strongly acidified by concentrated HCl, extracted with/

ether, the ether extracted with sodium carbonate and then the acid taken up into ether again. The ether left a semicrystalline product which melted at 213° after recrystallisation from dilute acetone.

(d) Action of ethylchlorocarbonate on O-N.diethyl-laurotetanine.

0.1 Gm. of O.N-diethyl-laurotetanine hydriodide were converted into the oily base and this base dissolved in chloroform (2 c.c.). Within one hour ethylchlorocarbonate (0.035 c.c.) and caustic soda (0.66 c.c. of a 0.984 N) were added twice. Shaking and cooling with ice is essential. Then chloroform and caustic soda were separated, the chloroform layer was repeatedly extracted with 15% acetic acid to remove any basic compounds, the chloroform then was dried and evaporated. The remaining oil solidified when standing in a desiccator over night. The crystals were first recrystallised from 50% acetic acid, then from dilute alcohol, m.p. 129-130º.

$C_{26}H_{33}O_6N$ calc. C = 68.57, H = 7.26

found C = 68.57, H = 7.43

(e) /

(e) Benzoylation of O-N-diethyl-laurotetanine.

The O-N-diethyl base (from 0.1 gm. of hydriodide) was treated with benzoyl chloride according to Späth (38). The brownish-yellow oil was distilled at 0.1 mm. The fractions 240-270° and 270-300° were collected separately and re-crystallised from ethyl acetate; they then melted at 138° (softening from 135°).

$C_{30}H_{33}O_5N$ calc. C = 73.92, H = 6.77

found C = 73.53, H = 6.58

(f) Hofmann degradation of 2-5-6 trimethoxy-3-ethoxy-N-ethyl-nor-aporphine (III).

This substance was put at my disposal by Dr Eisenbrand. The tartrate (0.1 gm. corresponding to 0.073 gm. of free base) was treated in exactly the same way as described above for the natural product. Owing to scarcity of material we did not purify specially any of the intermediate steps. 0.027 Gm. of 2.5.6-trimethoxy-3-ethoxy-8-vinyl-phenanthrene was obtained. It crystallised from alcohol in long, slightly greenish needles, absolutely different from the natural product. M.p. 141°(softening 139°) mixed m.p. with natural trimethoxy-ethoxy-8-vinyl-phenanthrene/

phenanthrene 133° (considerable softening from 129°).

4.054 mg. subst. 11.15 mg. CO_2 + 2.35 mg. H_2O

$C_{21}H_{22}O_4$ calc. C = 74.55, H = 6.51

found C = 75.01, H = 6.44

Above vinyl product (0.006 gm.) was oxidised with potassium permanganate (0.0096 gm.) as mentioned earlier. After recrystallising from dilute acetone the 2-5-6 trimethoxy-3-ethoxy-phenanthrene-8-carboxylic acid melted at 209°; when mixed with the natural substituted phenanthrene carboxylic acid it melted at 188°.

No results could be obtained from the interaction of benzoyl chloride and ethylchlorocarbonate on 2-5-6-trimethoxy-3-ethoxy-N-ethyl-nor-aporphine. The oily products were distilled in high vacuum repeatedly but could not be obtained in crystalline form.

(g) Hofmann degradation of 2-ethoxy-3-5-6-trimethoxy N-ethyl-nor-aporphine (IV)

0.09 Gm. hydriodide of the base IV (corresponding to 0.067 gm. of free base) were employed for the Hofmann degradation which was effected according to/

to the prescriptions given above. Owing to scarcity of material no intermediate stages were isolated in a state of absolute purity. 2-Ethoxy-3-5-6-trimethoxy-8-vinyl-phenanthrene crystallises from alcohol in slightly red plates with strong refraction which were very similar in form to the degradation product from natural sources.

M.p. 142°(softening 141°), mixed m.p. with the natural material 142° (within one degree); mixed m.p. with 2-5-6-trimethoxy-3-ethoxy-8-vinyl-phenanthrene 132° (softening from 125°). No doubt 2-ethoxy-3-5-6-trimethoxy-8-vinyl-phenanthrene is identical with the natural material.

3.574 mg. subst. 9.785 mg. CO_2, 2.10 mg. H_2O

$C_{21}H_{22}O_4$ calc. C = 74.55, H = 6.51

found C = 74.67, H = 6.58

(h) Action of ethylchlorocarbonate on 2-ethoxy-3-5-6-trimethoxy-N-ethyl-nor-aporphine.

The hydriodide of the base IV (0.050 gm. corresponding to 0.037 gm. free base) was treated with ethylchlorocarbonate as described earlier. The product was recrystallised from 50% acetic acid, then/

then from dilute alcohol. Probably owing to some impurities crystallisation was rendered rather difficult. M.p. 127-129°, mixed with the natural product (129-130°) it melted at 129°; there was no depression.

$C_{26}H_{33}O_6N$ calc. C = 68.57, H = 7.26.

found C = 68.45, H = 7.28.

(i) Benzoylation of 2-ethoxy-3-5-6-trimethoxy-N-ethyl-nor-aporphine.

The hydriodide of base IV (0.039 gm. corresponding to 0.028 gm. of the free base) were treated with benzoyl chloride as described earlier. The reaction product was distilled at 270° and 0.1 mm. After crystallising from ethyl acetate it melted at 138° (softening 136°); mixed m.p. with derivative of the natural product 138° (softening 134°).

I have thus been able to demonstrate that three derivatives of 2-ethoxy-3-5-6-trimethoxy-N-ethyl-nor-aporphine are identical with derivatives of natural laurotetanine, two derivatives of 2.5.6-trimethoxy-3-ethoxy-N-ethyl-nor-aporphine not being identical with the natural degradation products.

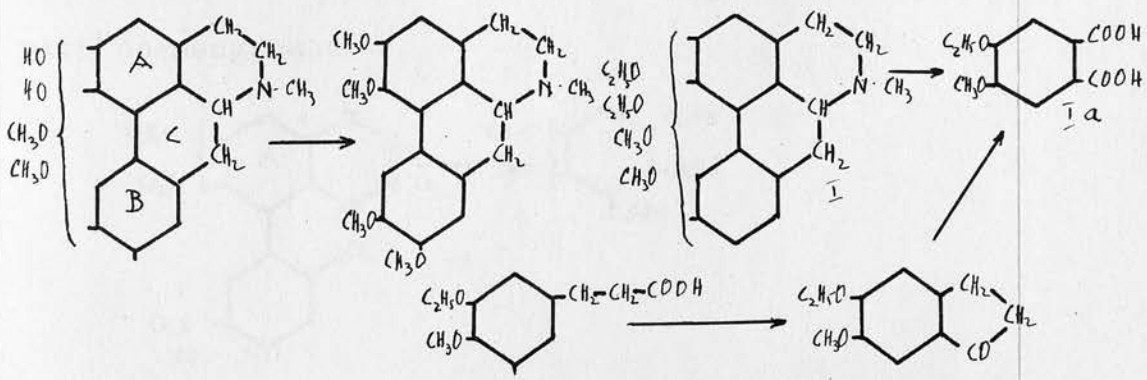
Laurotetanine/

Laurotetanine therefore is 2-oxy-3-5-6-trimethoxy-nor-aporphine as was assumed by Späth and Strauhal by analogy.

The Constitution of Boldine

A. Theoretical part.

Boldine has been isolated about 60 years ago from a South American shrub by Bourgoin and Verne (16). In spite of interesting physiological and pharmacological properties (98) practically nothing was known about the constitution. In 1922 pure boldine was prepared and some salts were analysed in the scientific laboratories of E. Merck of Darmstadt (99). Shortly afterwards Warnat (43) was able to show that boldine was a tertiary aporphine alkaloid and that by methylating boldine with diazomethane glaucine was obtained.

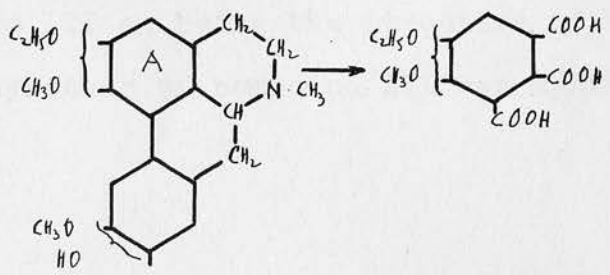


By oxidation with permanganate Warnat only obtained oxalic acid. He was unable to give any indications concerning the relative positions of the two hydroxyl and the two methoxyl groups.

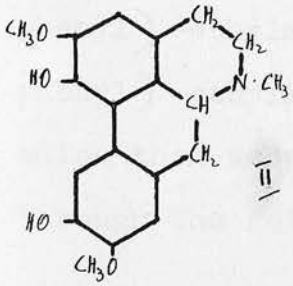
By oxidising boldine again I could only trace oxalic acid like Warnat. Boldine diethylether was then oxidised, methyl-ethyl-ether-nor-m-hemipinic acid being isolated in good yield.

This definitely proved Warnat's speculation that one hydroxyl and one methoxyl group must be attached to each benzene nucleus. As m-hemipinic acid is symmetrical no further conclusion about the respective arrangement could be drawn.

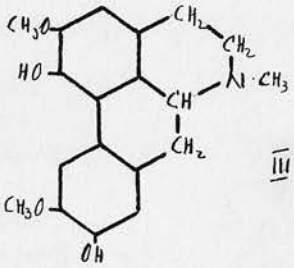
Analogous to a paper of Späth and Berger (51) on the constitution of corytuberine, boldine was ethylated with only one mol of diazoethane. In case that the hydroxyl in nucleus A is preferentially blocked by the ethyl group, a methoxy-ethoxy-benzene tricarboxylic acid could be expected when oxidised with permanganate.



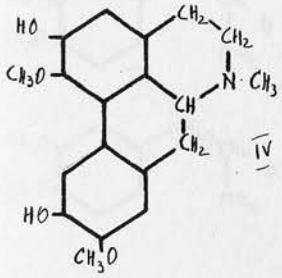
This experiment however failed, only the already mentioned m-hemipinic acid was isolated. Theoretically there were still four possibilities for the constitution of boldine left, viz.:



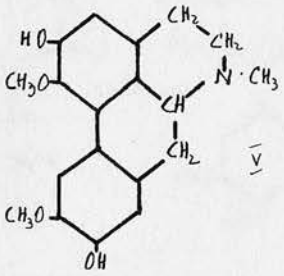
II



III



IV



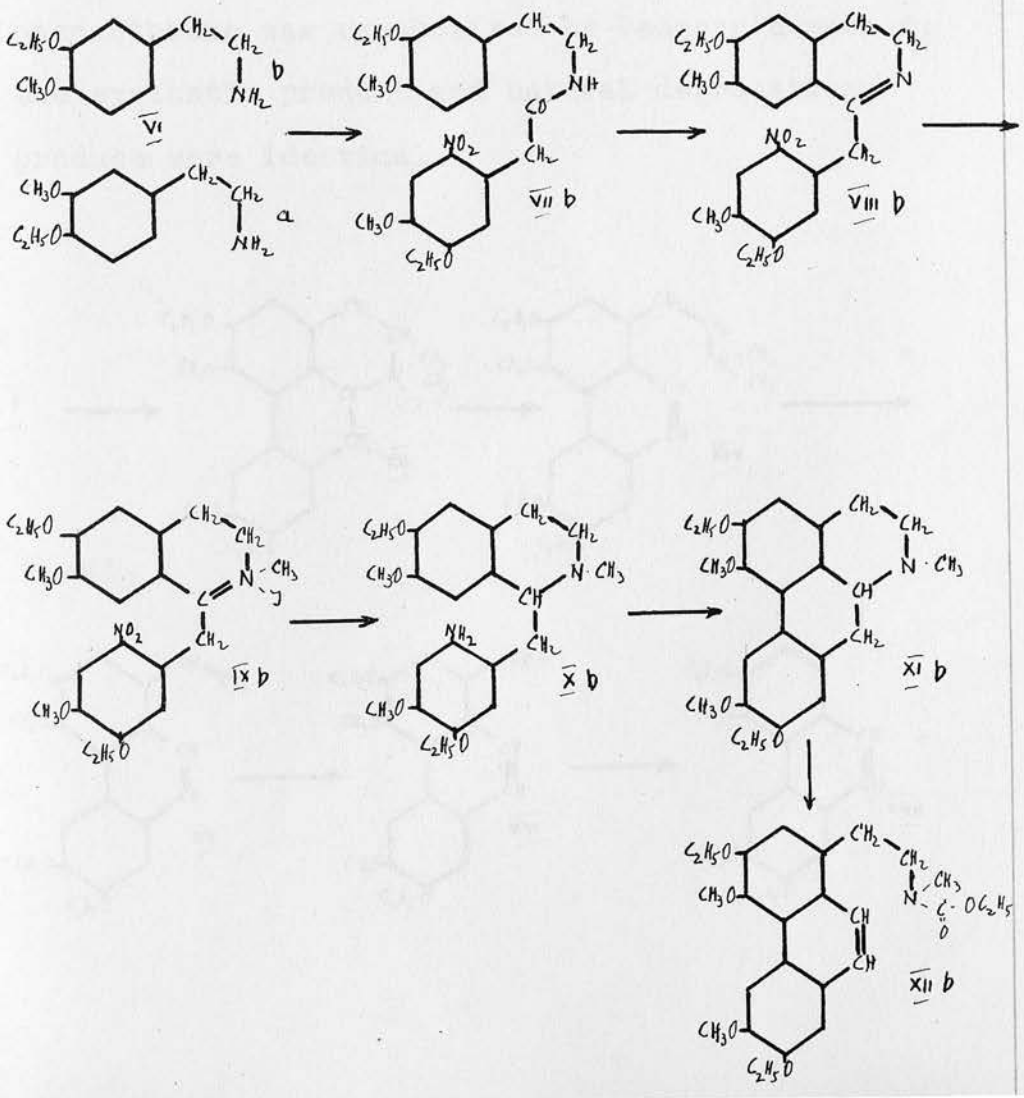
V

Laurotetanine being a derivative of isovanillin in its lower ring B, it seemed to be justified to propose a similar arrangement for boldine, thus excluding II and IV. In analogy to the structure of corytuberine (see earlier) the author first preferred III as being the structure of boldine. The diethylether of compound III was synthesised but

was/

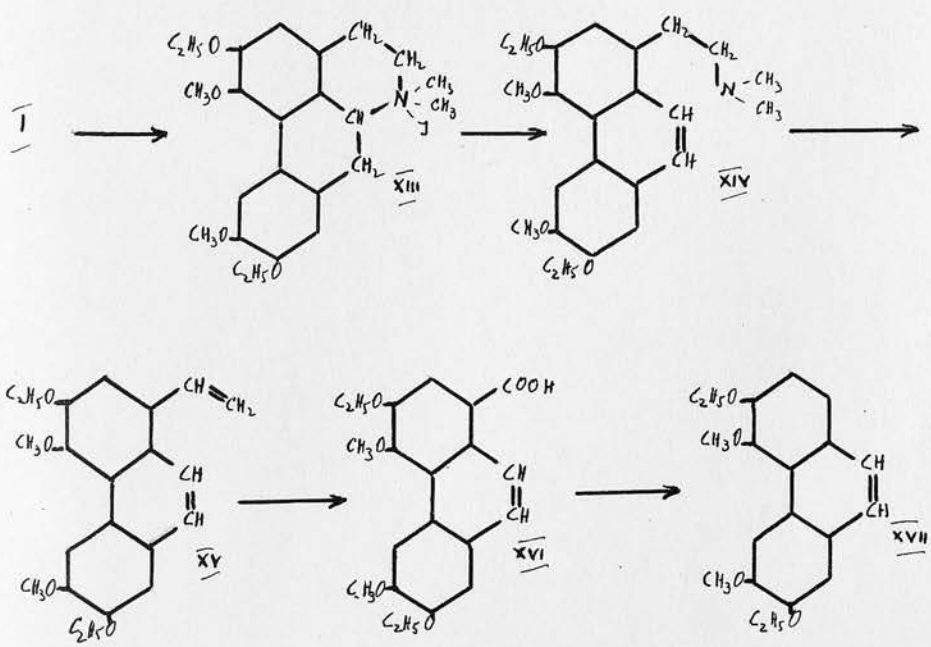
was not identical with boldine-diethylether. Then the diethylether of compound V was synthesised and was indeed identical with the natural product.

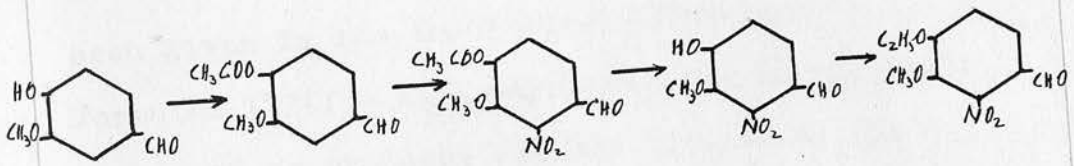
Starting with [3-ethoxy-4-methoxy-6-nitro-phenyl]-acetic acid, VI b., β-[3-methoxy-3-ethoxy-phenyl]-ethylamine (100) and β-[3-methoxy-4-ethoxy-phenyl]-ethylamine, two acid amides were obtained which then were converted to aporphine bases through the following stages:-

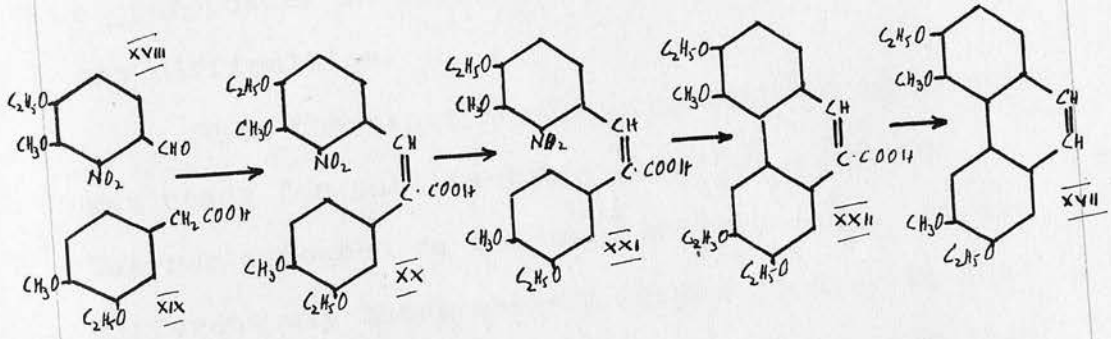


The N-ring, as in the case of laurotetanine, was opened with ethylchlorocarbonate, product XII b. was identical with the product from natural source. In the experimental part the intermediate steps for the synthesis of the diethylether of compound III are named VIIa - XII a.

As a second proof for the correctness of proposed structure the author then effected a Hofmann degradation on diethyl-boldine and finally obtained a dimethoxy-diethoxyphenanthrene. The phenanthrene was synthesised by Pschorr's method; the synthetic product and natural degradation products were identical.




HO
CH3O
CHO
CH3COO
CH3O
CHO
CH3COO
CH3O
CHO
NO2
HO
CH3O
CHO
NO2
C2H5O
CH3O
CHO
NO2


XVIII
C2H5O
CH3O
CHO
NO2
CH2COOH
CH3O
C2H5O
XIX
C2H5O
CH3O
NO2
CH
C·COOH
CH3O
C2H5O
XX
C2H5O
CH3O
NO2
CH
C·COOH
CH3O
C2H5O
XXI
C2H5O
CH3O
CH
C·COOH
C2H5O
C2H5O
XXII
C2H5O
CH3O
CH
CH
CH3O
C2H5O
XVII

The details of the Hofmann degradation have already been given in the theoretical introduction. Formulae XVIII - XXII represent the intermediate stages of an ordinary Pschorr synthesis, the carboxyl group of compound XXII was eliminated with copper-powder in quinoline solution (70) without any difficulties.

When the paper on the constitution of boldine was ready for publication a paper by Späth and Tharrer appeared on the same subject (44). In a different way these authors proved that V. is the constitution of boldine. For identification they also synthesised compound XVIII.

B. Experimental Part.

B. Experimental Part.

The author has to thank the firm of E. Merck of Darmstadt who most generously put a considerable quantity of boldine at his disposal. The alkaloid was recrystallised from chloroform and then melted at 162°.

(a) Ethylation of boldine and Hofmann degradation of diethyl boldine.

Boldine (2 gm.) was dissolved in absolute alcohol (20 c.c.) and an ethereal solution of diazoethane (from 5 c.c. of nitroso-N-ethyl-urethane was added. The following day the same amount of diazoethane was added again; after 6 hours the excess was destroyed by some drops of acetic acid. The ether was distilled off, the residue was taken up in dilute HCl. Caustic soda was added and the non-phenolic bases taken up into ether. From the ether residue the hydrochloride was prepared by adding alcoholic HCl and evaporating the excess in a desiccator. The hydrochloride was then taken up in a little water and treated with charcoal. By adding potassium iodide to this solution the diethyl-boldine hydriodide was precipitated. It may be recrystallised/

recrystallised from alcohol but it very much inclines to form a jelly. The free base is a yellow-brownish oil.

Dimethoxy-diethoxy-vinyl-phenanthrene.

The oily base (1.413 gm.) was dissolved in acetone, some drops of methyl iodide added and left standing for two days. Solvent and excess methyl iodide were removed in vacuo, a semi-solid compound was left behind XIII (1.280 gm.). It was dissolved in boiling water (128 c.c. + 5 c.c. of CH_3OH), caustic potash (6 gm.) was added, the whole being boiled under reflux for an hour. The resulting yellow oil (XIV) (0.969 gm.) was dissolved in methyl alcohol (3 c.c.), methyl iodide being added again and refluxed for an hour. Water (100 c.c.) was added and the organic solvent evaporated. The aqueous solution was treated with freshly precipitated silver chloride for an hour, filtered and the filtrate was concentrated to about 20 c.c. It was then treated with solid caustic potash (10 gm.) as mentioned above. Trimethylamine was evolved, the vinyl compound separated in crystalline condition. It was extracted with ether and recrystallised several times from alcohol/

alcohol. 0.34 gm. of pure vinyl compound, melting at 112-113° resulted (XV).

3.749 mg. subst. 10.31 mg. CO_2, 2.21 mg. H_2O

$C_{22}H_{24}O_4$. Calc. C = 75.00, H = 6.52.

Found C = 75.00, H = 6.60.

Dimethoxy-diethoxy-phenanthrene-carboxylic acid.

Above vinyl compound (0.311 gm.) was dissolved in purified acetone (37 c.c.) and 5 atoms of O in the form of potassium permanganate were added. The following day the acetone was evaporated, MnO_2 was dissolved by SO_2, some concentrated HCl was added and the aqueous solution was extracted repeatedly with ether. The ether was extracted by sodium carbonate solution leaving behind in the ether a considerable quantity of a yellow neutral fraction. NaCl was added to the aqueous solution; it was then acidified and extracted with ether again. The semi-solid ether residue was recrystallised once from benzene, but was not prepared in pure state (XVI).

Dimethoxy-diethoxy-phenanthrene

The carboxylic acid (0.050 gm.) was heated to boiling for ten minutes with copper powder (0.13 gm.) in quinoline (2.5 c.c.). Much ether was/

was added, the copper powder was filtered off and the ethereal solution was extracted about ten times with HCl until there was no more reaction of quinoline left. The ether was then washed with dilute NaOH, water, and then dried and evaporated, 0.039 gm. of crude crystalline material resulted. In high vacuum it distilled at about 180°; it was recrystallised twice from ether-petrolether (40-60°), the ethereal solution showed a blue fluorescence. The product then melted at 132-133° (XVII).

When mixed with the synthetic 3-5-dimethoxy-2-6-diethoxy-phenanthrene (m.p. 133°), it also melted at 133°. There was no depression.

(b) Synthesis of 3-5-dimethoxy-2-6-diethoxy-phenanthrene

The required starting materials were:

1. 2-nitro-3-methoxy-4-ethoxy-benzaldehyde(XIX).
2. 3-ethoxy-4-methoxy-phenylacetic acid (XVIII).

The second compound had been first prepared by Barger and co-workers (47) and subsequently by Späth; the first one was still unknown. This was prepared according to prescriptions of Pschorr and Sumuleanu (101) with the modifications given by Pisovski/

Pisovski (102),an ethyl group being introduced by means of diethylsulphate.

(1) Acetovanillin. Vanillin (40.2 gm.) was dissolved in 0.85 N KOH (333 c.c.) and acetic anhydride (26.4 c.c.) was added in portions. Acetovanillin soon separates in crystalline form; it was filtered, well washed and thoroughly dried.

(2) 2-Nitro-4-aceto-3-methoxy-benzaldehyde. Crude acetovanillin (56 gm.) was slowly added to fuming nitric acid (93 c.c., D = 1.4), the temperature was kept between 0 and 15°. The nitration product was then poured into a large volume of water, a solid separated which was well washed and dissolved in ether. The ether solution was washed again, dried and evaporated to one third. Petrol ether was then added; the wanted compound very soon separated in pure condition.

(3) 2-Nitrovanillin.was prepared according to the prescriptions of Pschorr and Pisovski by hydrolysing the acetyl group of above compound.

(4) 2-Nitro-3-methoxy-4-ethoxy-benzaldehyde.(2-nitro-vanillin-ethyl ether): 2-Nitrovanillin (17.4 gm./

gm.),NaOH (24.5 c.c. 15% sol.) and diethyl sulphate (20.54 c.c.) were first shaken at room temperature and then heated on the water bath for half an hour. Then the aqueous solution had to be only faintly alkaline. After cooling 2-nitro-3-methoxy-4-ethoxy benzaldehyde separated. It was recrystallised from dilute alcohol and then melted at 102-104°.

(5) (3-Ethoxy-4-methoxy-phenyl)-acetic acid (9.61 gm) was converted into the sodium salt which was dried at 100° in high vacuum for an hour. 2-Nitro-vanillin-ethylether (10.35 gm.) and acetic anhydride (48 c.c.) were added, the mixture was then heated under reflux for 63 hours, nitrogen being passed over the reaction mixture. Hot water (48 c.c.) was added and the acetic anhydride thus destroyed. Then another 50 c.c. of boiling water were added and the solution was filtered. After cooling the substituted nitrostilbene carboxylic acid (XX) separated. The dark brown residue was repeatedly extracted with dilute ammonia. On acidifying the filtered alkaline solution a further crop of the nitrostilbene carboxylic acid was collected.

The acid was recrystallised four times from methyl alcohol and then melted at 186-187° (XX).

(6)/

(6) The nitro-stilbene-carboxylic acid (XX) (1.99 gm.) was dissolved in 5% NH_3 (43.8 c.c.). Ferrous sulphate (8.78 gm.) was dissolved in water (22 c.c.) and concentrated ammonia (22 c.c.) was added. This mixture was heated on the free flame, simultaneously the solution of the nitrostilbene carboxylic acid was heated. When the temperatures had reached 91° the nitrostilbene carboxylic acid was quickly poured into the reduction mixture. It was then heated on the water bath for half an hour, the ferric hydroxide was then filtered off and the aminostilbene carboxylic acid was precipitated by 50% acetic acid. The amino acid was carefully dried and afterwards recrystallised from ether-petrol ether. It melted at 126°, yield 1.43 gm.

(7) The amino-stilbene carboxylic acid (0.85 gm.) was dissolved in methyl alcohol, 2 N sulphuric acid (8 c.c.) was added and the amino acid was diazotised by adding 1 N nitrite at 0°. The diazotised solution was left standing on ice for 15 minutes and at room temperature for one hour. Water (16 c.c.) was added and copper C-Kahlbaum (2 gm.) while shaking constantly. After two hours the reaction mixture/

mixture was heated to 70°, more water (50 c.c.) added, the solution was made alkaline by ammonia, the copper bronze was filtered off. The aqueous solution showed a blue coloration; it was acidified and taken up in ether, the colour being straw-yellow then. The ether solution was dried and concentrated. Standing in the ice-chest over-night the dimethoxy-diethoxy-phenanthrene carboxylic acid separated. It was recrystallised from alcohol and then melted at 222-223°, yield 0.144 gm.

(8) Dimethoxy-diethoxy-phenanthrene carboxylic acid was decarboxylated as described above for the phenanthrene carboxylic acid obtained by Hofmann degradation of boldine diethylether. Dimethoxy-diethoxy-phenanthrene was recrystallised from ether petrolether, it separated in faintly yellow needles, melting at 134°, giving no melting point depression when mixed with the substituted phenanthrene obtained by Hofmann degradation of boldine diethyl-ether.

(c) Action of ethylchlorocarbonate on diethylboldine.

The oily boldine diethyl ether (0.077 gm.) was dissolved in chloroform (5 c.c.). To the well cooled solution ethylchlorocarbonate (0.05 c.c. and/

and N/10 NaOH (5.73 c.c.) were added twice in the course of an hour. The chloroform was separated, washed with HCl and water, dried and evaporated. The crystalline residue was recrystallised from dilute alcohol, 40% acetic acid and dilute alcohol again. It then melted at 115-116° (XII C)

3.966 mg. subst. 10.005 CO_2, 2.575 mg. H_2O

$C_{26}H_{33}O_6N$ Calc. C = 68.57, H = 7.25

Found C = 68.81, H = 7.27

The N-benzoyl product, prepared by interaction of diethyl boldine and boiling benzoyl chloride was an oil which could not be crystallised.

(d) Oxidation of boldine-diethyl-ether.

The oily base (0.369 gm.) was dissolved in dilute HCl, NaOH was added until turbidity occurred. At room temperature a 1% potassium permanganate solution was added in portions of 20 c.c. Thus 90 c.c. of permanganate were used, oxidation was then continued on the water bath; 180 c.c. of permanganate were added in all. Manganese dioxide was dissolved by SO_2, the aqueous solution was concentrated to 50 c.c. in vacuum, acidified with HCl/

HCl and extracted in an extractor. The ether residue was dissolved in very dilute ammonia, to the hot solution a hot solution of calcium chloride was added. Small amounts of calcium oxalate were filtered off, the acidified solution was exhausted with ether in an extractor for the second time. The ether residue was dissolved in a few drops of acetone and put into a distilling bulb (Kugelrohr?), it was then distilled in high vacuum. A first small fraction distilled at about 115°, it crystallised and melted at 103-108°. The main fraction distilled at 150-190° (yellow crystals), after repeated sublimination it melted at 186°. This fraction was three times evaporated with an alcoholic ethylamine solution in a distilling bulb, for 5 minutes it was heated to 100° and for another 5 minutes to 180°. Afterwards it was distilled in high vacuum at 130-150°. After recrystallising twice from methyl alcohol the melting point was 201-202°, the crystals were faintly yellow.

2.146 mg. subst. 4.91 mg. CO_2, 1.09 mg. H_2O

$C_{13}H_{15}O_4N$ Calc. C = 62.65, H = 6.02

Found C = 62.49, H = 5.69.

We suspected the substance to be methyl-ethyl-ether/

ether-nor-m-hemipinic acid (Ia), which was therefore systhesised as follows(see page 56).

[β- 4-methoxy-3-ethoxy-phenyl] -propionic acid (1 gm. see later) was converted into the corresponding hydrindone by boiling with P_2O_5 in benzene solution (103). The crude hydrindone (0.454 gm.) was heated on the water bath with nitric acid (6.5 c.c. of D = 1.2) for 3 hours. The solutionwas then filtered, neutralised by potassium carbonate and acidified slightly by adding HCl. It was then extracted with ether in an extractor. The ether residue was distilled in high vacuum, treated with ethylamine solution as before, distilled in high vacuum again and recrystallised twice from methyl alcohol. The melting point was 202.5°, there was no depression when mixed with the ethylimide of the oxidation product from boldine diethylether.

Syntheses/

(e) Syntheses of the two phenylethylamines (VIa, VIb)

The two substituted phenylethylamines were prepared by Hofmann degradation of the corresponding β-phenylpropionamides; all the intermediate steps were new compounds.

1a. 3-methoxy-4-ethoxy-cinnamic acid was prepared from ethylvanillin and malonic acid in pyridine solution. Yield 90%, m.p. 200-201° (recryst. from ethyl alcohol).

3.984 mg. subst. 9.49 mg. CO_2 , 2.28 mg. H_2O

$C_{12}H_{14}O_4$ Calc. C = 64.86, H = 6.31

Found C = 64.97, H = 6.4.

1b. 4-Methoxy-3-ethoxy-cinnamic acid from ethyl-isovanillin and malonic acid in pyridine solution. Yield 90%, m.p. 176° (from ethyl alcohol).

3.826 mg. subst. 9.095 mg. CO_2, 2.175 H_2O.

$C_{12}H_{14}O_4$ Calc. C = 64.86, H = 6.31

Found C = 64.83, H = 6.36.

2a. (3-Methoxy-4-ethoxy-phenyl) propionic acid was prepared from 1a by catalytic hydrogenation with Pd-calcium carbonate catalyst in alkaline solution/

solution. Yield almost quantitative, m.p. 130° (from chloroform-ligroin).

4.256 mg. subst. 10.025 mg. CO_2, 2.74 H_2O

$C_{12}H_{16}O_4$ Calc. C = 64.28, H = 7.14.

Found C = 64.24, H = 7.20.

2b. [4-Methoxy-3-ethoxyphenyl] -propionic acid was prepared in the same way from acid 1b. Yield almost quantitative, m.p. 105.5° (from chloroform-ligroin).

4.133 mg. subst. 9.755 mg. CO_2, 2.66 mg. H_2O

$C_{12}H_{16}O_4$ Calc. C = 64.28, H = 7.14

Found C = 64.37, H = 7.20.

3a. [3-Methoxy-4-ethoxyphenyl] -propionamide was prepared from the acid chloride and concentrated ammonia. The yield was between 40 and 60%, m.p. 128° (not sharp).

3b. The yield of amide 3a was not satisfactory; it also differed in various runs (104); this amide therefore was prepared in a different way. Acid 2b. (26 gm.) were heated to boiling for 5 hours with absolute alcohol (75 c.c.), toluene (125 c.c.), and concentrated/

concentrated sulphuric acid (5 c.c.). Part of the solvent was then removed by distillation (100 c.c.), the aqueous solution was separated, the toluene was washed with dilute sodium carbonate and then dried. The toluene was distilled off, ethyl-4-methoxy-3-ethoxy-phenyl-propionate being distilled under reduced pressure. B.p. 187° (16.5 mm.). Yield 21-22 gm. The ester (18 gm.) was shaken with concentrated ammonia (104) (50 c.c. of D = 0.88) for 5 days and then left standing in the stoppered bottle for 4 weeks. The amide then separated in very pure condition, yield 85%, m.p. 123° (from benzene).

4.069 mg. subst. 9.58 mg. CO_2, 2.66 mg. H_2O

$C_{12}H_{17}O_3N$ Calc. C = 64.57, H = 7.62

Found C = 64.21, H = 7.31.

4a. β-〔3-Methoxy-4-ethoxy-phenyl〕ethylamine. The Hofmann degradation was carried out with the calculated amount of hypochlorite, the special conditions for this reaction have been studied in detail by Decker (105). When working very carefully a yield of 67% was obtained. The product was distilled in vacuum, it was a colourless oil with amine-like odour, b.p. 156°/11 mm.

4b. [β-Methoxy-3-ethoxy-phenyl] -ethylamine was prepared similarly, b.p. 158°/12.5 mm., colourless oil with amine-like odour.

Compounds 4a and 4b have been prepared earlier by Späth and Dobrowski (100) in another way. Both amines were coupled with the chloride of 3-ethoxy-4-methoxy-6-nitrophenylacetic acid. The author wishes to express his indebtedness to Dr and Mrs Eisenbrand of Berlin who kindly supplied this acid.

(f) Synthesis of compound XIa and compound XIIa:

VIIa. N- [β-(3-methoxy-4-ethoxy-phenyl) ethyl] -3-ethoxy-4-methoxy-6-nitro-phenacetamide was obtained when working according the prescriptions given by Barger and co-workers (47). The yield was 52%, m.p. 164.5-165° (from methyl alcohol).

4.303 mg. subst. 9.53 mg. CO_2, 2.475 mg. H_2O

$C_{22}H_{28}O_7N_2$ Calc. C = 61.10, H = 6.48.

Found C = 60.40, H = 6.44.

VIIIa. 1- [3-Ethoxy-4-methoxy-6-nitro-benzyl] -6-methoxy-7-ethoxy-3-4-dihydro-isoquinoline was obtained in a yield of 78% (57). M.p. 177-178°, recryst. from ethyl alcohol.

4.082/

4.082 mg. subst. 9.57 mg CO_2, 2.24 mg. H_2O

$C_{22}H_{26}O_6N_2$ Calc. C = 63.77, H = 6.28.

Found C = 63.94, H = 6.14.

IXa. 1- [3-Ethoxy-4-methoxy-6-nitro-benzyl] -6-methoxy-7-ethoxy-3-4-dihydro-isoquinoline methiodide was prepared by heating the free base in a sealed tube with excess of methyliodide to 100° for 20 min. The product was first recrystallised from water, then from alcohol, m.p. 198-199° (decomp.), yield almost quantitative.

4.273 mg. subst. 7.77 mg. CO_2, 2.005 mg. H_2O

$C_{23}H_{29}O_6N_2I$ Calc. C = 49.64, H = 5.22

Found C = 49.59, H = 5.25

Xa. 1- [3-Ethoxy-4-methoxy-6-amino-benzyl] 2-methyl 6-methoxy-7-ethoxy-tetrahydro-isoquinoline was obtained by reduction of compound IXa by means of zinc dust and hydrochloric acid. Picrolonic acid has been found to be very useful for isolation of this base (106). Yield 65%. By treating with concentrated sulphuric acid and methyl alcohol the free base may be prepared again, thus at least 90% of the picrolonic acid was regenerated.

XIa /

XIa. 2-5-Diethoxy-3-6-dimethoxy-aporphine was prepared according to Pschorr's method. The crude base Xa, regenerated from the picronolate, was diazotised with barium nitrite. The yield of aporphine compound was minute (5-10%); it was isolated as sparingly soluble hydriodide (56). The hydriodide may be recrystallised from ethyl alcohol, but as we only possessed 0.04 gm. approximately we did not purify it thoroughly.

XIIa. Action of ethylchlorocarbonate on 2-5-diethoxy-3-6-dimethoxy-aporphine (47): The oily base (0.037 gm.) was dissolved in chloroform (5 c.c.) and the solution well cooled in ice. Within an hour twice were added ethylchlorocarbonate (0.021 c.c.) and caustic soda (3.2 c.c. N/10). The pro/duct of the reaction was worked up as recorded earlier (47) and recrystallised twice from dilute alcohol, m.p. 106-107°.

3.558 mg. subst. 8.905 mg. CO_2, 2.29 mg. H_2O

$C_{26}H_{33}O_6N$ Calc. C = 68.57, H = 7.25

Found C = 68.26, H = 7.20

Synthesis/

(g) Synthesis of r-boldine-diethyl-ether (XIb and XIIb)

VIIb. N-(β-(4 methoxy-3-ethoxy-phenyl)-ethyl)-3-ethoxy-4-methoxy-6-nitro-phenacetamide was prepared in the same way as compound VIIa. Yield 50%, m.p. 157.5° (from methyl alcohol).

4.051 mg. subst. 9.065 mg. CO_2, 2.32 mg. H_2O

$C_{22}H_{28}O_7N_2$ Calc. C = 61.10, H = 6.48

Found C = 61.03, H . 6.41.

VIIIb. 1-(3-ethoxy-4-methoxy-6-nitro-benzyl)-6-ethoxy-7-methoxy-3-4-dihydro-isoquinoline was prepared like compound VIIIa. Yield 76%, m.p. 163.5 (from ethyl alcohol), the crystals were more yellow than compound VIIIa.

4.125 mg. subst. 9.69 mg. CO_2, 2.32 mg. H_2O

$C_{22}H_{26}O_6N_2$ Calc. C = 63.77, H = 6.28.

Found C = 64.06, H = 6.29.

IXb. 1-(3-ethoxy-4-methoxy-6-nitro-benzyl)-6-ethoxy-7-methoxy-3-4-dihydro-isoquinoline-methiodide was prepared by heating base VIIIb with methyliodide to 100° in a sealed tube. Yield almost quantitative, recryst. from water, then from ethyl alcohol, m.p. 188° (decomp.).

Xb. 1- [3-ethoxy-4-methoxy-6-amino-benzyl] -2-methyl-6-ethoxy-6-methoxy-tetrahydro-isoquinoline was prepared in the same way as compound Xa. The base was purified over the picronolate, the yield was 90%.

XIb. 2-6-Di-ethoxy-3-5-dimethoxy-aporphine was prepared by Pschorr's method from compound Xb. From 0.51 gm. dipicronolate of base Xb. 0.042 gm. hydriodide of the aporphine was obtained.

XIIb. Action of ethylchlorocarbonate on 2-6-di-ethoxy-3-5-dimethoxy-aporphine: The oily aporphine base (0.029 gm.) was dissolved in 5 c.c. of chloroform and the solution well cooled in ice. Twice within an hour were added ethylchlorocarbonate (0.016 c.c.) and caustic soda (2.49 c.c. N/10). The product of the reaction was worked up as recorded earlier, after twice recrystallising from dilute alcohol, the compound melted at 114-115°.

2.949 mg. subst. 7.445 mg. CO_2, 1.90 mg. H_2O

$C_{26}H_{33}O_6N$ Calc. C = 68.57, H = 7.25

Found C = 68.85, H = 7.21

The/

The corresponding derivative of boldine-diethylether (comp. p. 71) like the synthetic product XIIb. melted at 115°, there was no depression when both compounds were mixed. The mixed melting point of the natural product and of compound XIIa (m.p. 106°) was 98°.

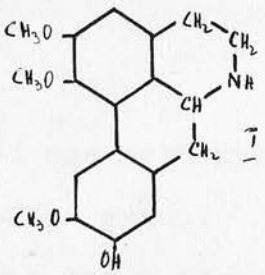
The alkaloid boldine therefore is 2-6-dihydroxy-3-5-dimethoxy-aporphine.

The Constitution of Actinodaphnine.

A. Theoretical Part.

Greshoff (19) discovered the wide distribution of the alkaloid laurotetanine in the N.O. Lauraceae. He isolated it first from Litsea chrysocoma Bl. but also mentions its presence in the genera Tetranthera (T. citrata Nees), Notaphoebe, Aperula and Actinodaphne (A. procera Nees). Although laurotetanine seems to be widely distributed in this order, Greshoff's work leaves some doubt as to whether it was always laurotetanine which he isolated.

Chopra (22) mentions that in British India alone about 60 species of Litsea are still uninvestigated (comp. p.8) so that the discovery of a new alkaloid actinodaphnine from Actinodaphne hookeri (N.O. Lauraceae) by Krishna and Ghose (23) was of interest in this connection.



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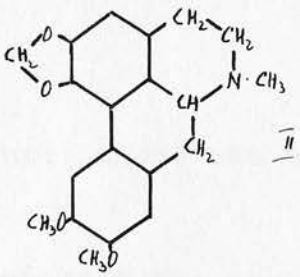


II

This base was certainly different from laurotetanine (I) and the authors discussed a similarity with bebeerine (107) without adopting any final conclusions. On the other hand it seemed to be more likely that actinodaphnine was closely related to laurotetanine, the latter having been isolated from another species of the same genus.

Dr S. Krishna of the Forest Research Institute at Dehra-Dun (British India) put at my disposal 23 grams of crude actinodaphnine and several grams of the purified material. I started again to work on the constitution of actinodaphnine and with this large supply of the base was able to determine its constitution apart from a slight doubt as to the respective positions of the methoxy and the phenolic hydroxy group.

The micro-analyses of the free base and also of a large number of degradation products led me to prefer $C_{18}H_{17}O_4N$ to the formula $C_{18}H_{19}O_4N$ recorded earlier; also the methoxyl estimation indicated/

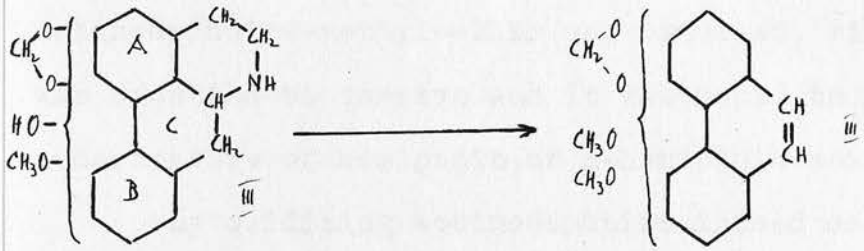
indicated one methoxyl group; there was no evidence for a N-CH_3- group.

The two O atoms previously not accounted for are present in a methylenedioxy group (Gaebel's test); positive evidence was obtained that actinodaphnine is a secondary base by the formation of a phenylthiocarbamide (20).

The Hofmann degradation did not offer any difficulties; after twice treating with methyliodide and caustic soda the nitrogen was eliminated as trimethylamine, thus showing that the nitrogen belongs to one ring only. The methine base was optically inactive and beautifully crystalline, the latter feature indicated that the new alkaloid must be related to glaucine or laureline as these bases yield the only two crystalline methine bases known (55, 18).

The melting points of the methine, the vinyl product and the corresponding phenanthrene were exceptionally high, suggesting a relationship to the aporphine alkaloid dicentrine (II). Dicentrine possesses the highest melting point of all the fully methylated aporphine alkaloids, probably due to the symmetrical/

symmetrical arrangements of its substituents. So far as we could trace the results of a Hofmann degradation on dicentrine have never been published[x] (108) but we assumed that its degradation products would probably also have rather high melting points.



III

Hofmann degradation: compare theoretical introduction.

By oxidising actinodaphnine methine with nitric acid (see theoretical introduction, p. 23) mellophanic acid was obtained. The isolation of that acid as its tetramethyl ester indeed confirmed the assumption that actinodaphnine is an aporphine base. The tetramethyl ester was compared with an authentic specimen prepared from pukateine.

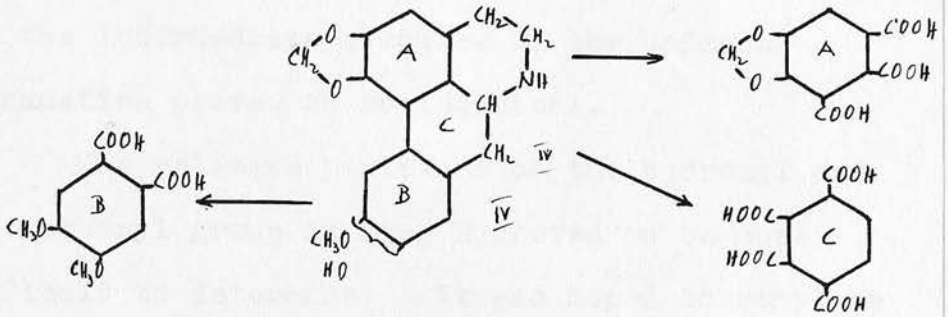
In/

[x] Meanwhile published by Manske.

In the first communication on actinodaphnine (23) it has already been stated that actinodaphnine contains one methoxyl and one hydroxyl group. According to the general outlines given in the theoretical introduction on oxidation of aporphine alkaloids with potassium permanganate, ring A was expected to yield methylene dioxyhemimellitic acid when actinodaphnine itself was oxidised. When actinodaphnine-methyl-ether was oxidised, ring B was expected to survive and it was hoped to isolate a derivative of hemipinic or m-hemipinic acid.

By oxidising actinodaphnine indeed methylene dioxyhemimellitic was obtained, its trimethyl ester was identified with an authentic specimen obtained by oxidation of pukateine. This acid has previously been prepared by Späth and Kuffner from bulbocapnine (79). Oxidation of the fully methylated actinodaphnine yielded m-hemipinic acid, isolated as ethylimide. We also compared this compound with an authentic specimen.

These results left little doubt about the constitution of actinodaphnine and at this stage the following formula was accepted:



The methylene-dioxy group is certainly in ring A, but an arrangement in 6:7 instead of 5:6 might still be possible, since such an arrangement is considered to be present in domesticine (31). (Comp. theoretical introduction, p.28). The methoxyl and the hydroxyl group must be in ring B, for only positions 2-3 can give rise to m-hemipinic acid. For the time being CH_3O in 3- and OH in 2-position was preferred, so that actinodaphnine would be a derivative of isovanillin. This hypothesis, first used by Späth and Strauhal (46), was recently found to be correct in both laurotetanine and boldine.

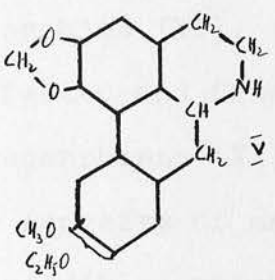
The position of the substituents in ring A was easily determined; by methylating actinodaphnine fully dicentrine was obtained. The melting points were identical and the same as that of a mixture,

all/

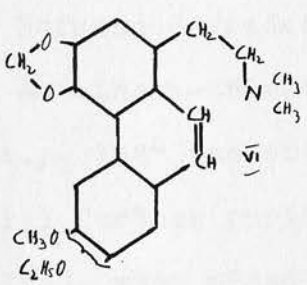
all the intermediate products of the Hofmann degradation proved to be identical.

The relative positions of the hydroxyl and the methoxyl group in ring B proved to be more difficult to determine. It was hoped to ethylate the phenolic OH- group thus differentiating it from the methoxyl group originally present. It was then intended to split off the methylenedioxy group with 50% sulphuric acid and phloroglucinol, a method worked out in detail by Späth and Quietensky (109) and subsequently employed with success by Späth and co-workers.

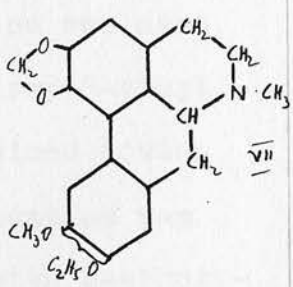
The results with O-ethyl-actinodaphnine (V) or O-ethyl-actinodaphnine-methine (VI) did not prove to be satisfactory, but better results were obtained with O-ethyl-N-methyl-actinodaphnine (VII).



V

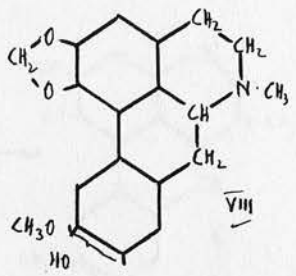


VI

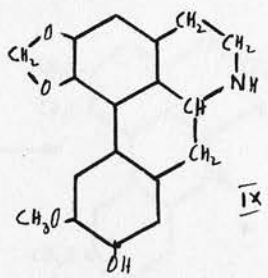


VII

In spite of the poor yield, we prepared O-ethyl-N-methyl-actinodaphnine, because we suspect it to be the ethylether of an alkaloid (VIII) which we hope soon to demonstrate in the crude alkaloid mixture from the bark of Actinodaphne hookeri.



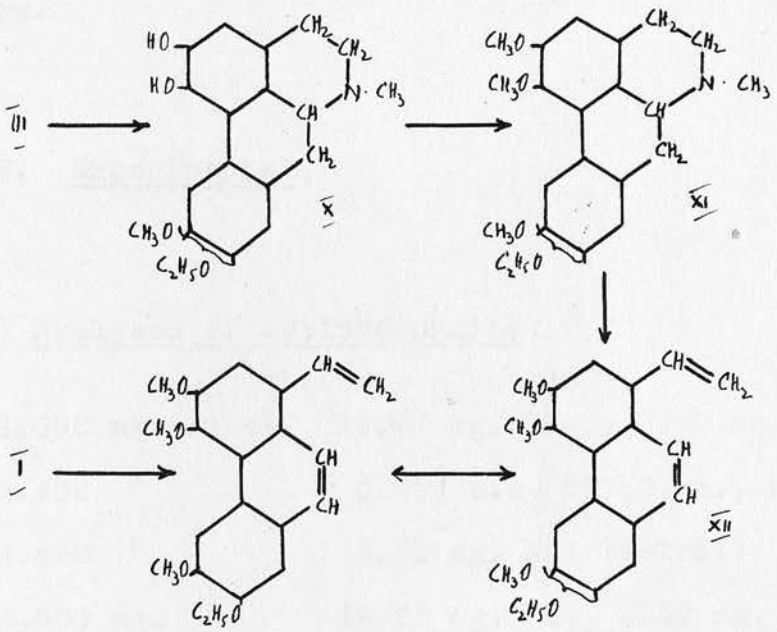
VIII



IX

The methylenedioxy group was split off, the dihydroxy compound (X) being beautifully crystalline. Owing to scarcity of material it was not prepared in analytically pure state but at once methylated with diazomethane thus obtaining an ethoxy-trimethoxy-aporphine (XI). A Hofmann degradation was next effected and finally an ethoxy-trimethoxy-8-vinyl phenanthrene (XII), m.p. 134° was obtained (owing to scarcity of material further purification was impossible) which melted, when mixed with 2-ethoxy-3-5-6-trimethoxy-8-vinyl-phenanthrene from laurotetanine (m.p./

(m.p. 142°) at 135°. When mixed with 3-ethoxy-2-5-6-trimethoxy-8-vinyl-phenanthrene a strong depression in the melting point occurred.



Formula IX is therefore proposed, actinodaphnine being 2-hydroxy-3-methoxy-5-6-methylene-dioxy-nor-aporphine. As the synthetic product XII gave a very slight depression with an authentic specimen from laurotetanine, we are engaged in the synthesis of product VII (C_2H_5O = 2, CH_3 = 3) which synthesis will be the final test of the correctness of our view.

B. Experimental.

(1) Analyses of actinodaphnine:

4.006 mg. subst. 10.20 mg. CO_2, 2.00 mg. H_2O (Roth)

5.432 " 0.227 c.c. N(753 mm., 26°) "

4.658 " 3.81 mg. AgI (Feisal) "

5.003 mg. 12.75 mg. CO_2, 2.47 mg. H_2O (Schoeller)

$C_{18}H_{19}O_4N$ C = 69.01, H = 6.07, N = 4.47 (original formula)

$C_{18}H_{17}O_4N$ Calc.
C = 69.45, H = 5.47, N = 4.50, CH_3O = 10.0

Found C = 69.44, H = 5.52, N = 4.62, CH_3O = 10.8 (Roth)

Found C = 69.52, H = 5.48 (Schoeller)

(2) Methylenedioxy group: Actinodaphnine (20 mg.) and phloroglucinol (60 mg.) were heated with 40% sulphuric acid (5 c.c.) in a water bath. Simultaneously tests with methylpukateine, glaucine and a blank were carried in the same vessel. After 20 min. the test tubes containing actinodaphnine and methylpukateine showed a bulky red precipitate, glaucine and the blank test showed merely a yellow coloration.

(3) Nitrogen atom: The Herzig-Meyer estimation was absolutely negative. It was then concluded that actinodaphnine was a secondary base like laurotetanine. The free base (22 mg.) was dissolved in absolute alcohol and phenyl-iso-thiocyanate (10 mg.) in a little alcohol was added (21). After two hours no crystals had formed; the solution was therefore concentrated to half its volume when the product soon began to crystallise; the crystals were very similar to the phenyl-thio-carbamide of laurotetanine. M.p. 181° (from alcohol).

5.052 mg. subst. 2.456 mg. $BaSO_4$.

S calc. 7.41.
found 6.67.

(4)/

(4) Phenolic hydroxyl group: The phenolic hydroxyl group previously recorded can easily by methylated with diazomethane. Actinodaphnine (2.16 gm.) was suspended in absolute methyl alcohol and a concentrated ethereal solution of diazomethane (from 7 c.c. of nitroso-N-methylurethane) was added. After standing for 8 hours diazomethane and ether were distilled off, ether again added and the basic compounds extracted with 2N HCl. The hydrochloride of the methylated base is sparingly soluble and usually separates during the extraction. The non-phenolic base was removed by ether from a sodium hydroxide solution; it is a yellow oil which inclines to crystallise. We did not prepare it in pure state, but transformed this compound at once into the sparingly soluble hydrochloride or sulphate, which can be recrystallised from either alcohol or water. There was no evidence that diazomethane also methylated the nitrogen (46, 110).

(5) Hofmann degradation: O-methyl-actinodaphnine (1.336 gm.) was dissolved in methyl alcohol (30 c.c.), methyl iodide (13.4 c.c.) was added and after

every/

every 2 hours sodium methoxide (9.8 c.c. of 0.023N solution) three times in all. After standing for 2 days the solvent was evaporated under reduced pressure and the residue dissolved in hot water. To the filtered solution potassium iodide and some ethyl alcohol were added, when the methiodide separated in almost colourless crystals. Re-crystallised from water or better from ethyl alcohol, they melted at 214° without decomposition.

The methiodide (1.272 gm.) was dissolved in boiling water (80 c.c.) and then solid caustic potash (15 gm.) was added. The whole was boiled under reflux for an hour, the methine soon began to separate in crystalline form, the mother liquor was coloured slightly red. Concentrated hydrochloric acid was added until the solution was only slightly alkaline, the precipitate of the methine was filtered, well washed with water and dried. The methine shows a blue fluorescence in acetone and a strong orange coloration with concentrated sulphuric acid; recrystallised twice from ethyl alcohol, m.p. 158-159°. The methine hydrochloride is sparingly soluble in water.

4.008 mg. subst. 10.51 mg. CO_2, 2.35 mg. H_2O

$C_{21}H_{23}O_4N$ Calc. C = 71.39, H = 6.52

Found C = 71.51, H = 6.56

The methine (from 0.2 gm. of hydrochloride) was dissolved in a few c.c. of methyl alcohol and an excess of methyl iodide added, the solution was heated under reflux for 5 minutes and then left standing for 2 hours. Boiling water (50 c.c.) was added and the organic solvent removed by heating on the water-bath. Freshly prepared silver chloride was added, the solution heated on the water-bath for another 30 minutes and the precipitate of silver chloride and iodide filtered off. The clear solution was concentrated to about 7 c.c. and solid caustic potash (3 gm.) was added. A brisk evolution of trimethylamine took place. As soon as it had stopped, the alkaline solution was extracted with chloroform. The chloroform was washed with dilute hydrochloric acid and water, dried and evaporated. The crystalline residue (0.131 gm.) was recrystallised several times from chloroform-absolute alcohol. It is very sparingly soluble/

soluble in absolute alcohol and ether. M.p. 205.5-206°.

3.995 mg. subst. 10.84 mg. CO_2, 1.78 mg. H_2O

$C_1 H_{16} O_4$ VI Calc. C = 74.02, H = 5.20

Found C = 74.00, H = 4.99

To this vinyl compound (0.074 gm.), dissolved in acetone (20 c.c.) and chloroform (20 drops) a solution of potassium permanganate (0.13 gm.) in acetone (30 c.c.) was added. Next day the manganese dioxide was filtered off and well washed with hot water. Washings were added to the acetone solution and the organic solvent was evaporated. The acidified solution was repeatedly shaken with ether, which left 0.041 gm. of a crystalline substance which was recrystallised once from benzene but was not obtained analytically pure.

Above phenanthrene-carboxylic acid (0.025 gm.) was heated with copper powder (0.19 gm.) in quinoline (2 c.c.) for 30 minutes. After dilution with ether, the copper was filtered off, the ethereal solution extracted about ten times with dilute HCl, then twice with dilute NaOH. The ether residue was sublimed in high vacuum at 165-175° and had a m.p. of/

of 204-205°. The pale yellow substance was re-crystallised from ether-petrolether and then melted at 206-208°.

2.808 mg. subst. 7.410 mg. CO_2, 1.305 mg. H_2O

$C_{17}H_{14}O_4$ Calc. C = 72.34, H = 4.96

Found C = 71.97, H = 5.20.

(6) Oxidation experiments.

(a) Oxidation of O-methyl-actinodaphnine-methine to mellophanic acid: The methine (0.889 gm.) was oxidised with concentrated nitric acid. The tetramethyl ester of the resulting acid, mixed with tetramethyl-mellophanate (from pukateine) melted without depression at 129°.

(b) Oxidation of actinodaphnine with potassium permanganate: Crude actinodaphnine (1.599 gm.) was dissolved in very dilute HCl and sodium carbonate added until slight turbidity occurred. A 4% solution of potassium permanganate was added in volumes of 4.26 c.c. (1/3 O) at a time. About 12 atoms of oxygen were used up at room temperature, the oxidation was then completed on the water bath, requiring 28 atoms of oxygen in all. The filtered solution/

solution was concentrated in vacuo to about 20 c.c., the filtered manganese dioxide added again and the whole heated on the water-bath with caustic potash (5 gm.) for 6 hours. Basic vapours with amine-like odour were evolved copiously. When the evolution had stopped the manganese dioxide was dissolved by SO_2 and large amounts of inorganic matter filtered off. The solution was then acidified with concentrated HCl and extracted with ether in a continuous extractor; after 17 hours the ether was evaporated and the residue thoroughly dried in a desiccator. The dried crystals were suspended in a little ether and a concentrated solution of diazomethane was added. After a few hours the excess of diazomethane was destroyed by acid, the ether washed with a little very dilute sodium carbonate to remove unchanged acid, and then evaporated. The ester distilled at 170-180°/0.07 mm. The distillate was dissolved in methyl alcohol, on cooling a small amount of a much higher melting substance (190-195°) separated first which was removed by filtration. A very small amount of water was added. After a short time the desired substance, the trimethylester of methylenedioxy-hemimellitic acid separated. After two

recrystallisations/

recrystallisations from slightly diluted methyl alcohol the m.p. was 128-129°. The ester gave a positive reaction for a methylenedioxy group when heated with phloroglucinol and sulphuric acid.

4.129 mg. subst. 8.08 mg. CO_2, 1.56 mg. H_2O

$C_{13}H_{12}O_8$ Calc. C = 52.70, H = 4.05

Found C = 53.37, H = 4.24.

(c) Oxidation of pukateine: In order to obtain an authentic specimen of methylenedioxy-hemimellitic acid pukateine was oxidised in the same way. After several recrystallisations the m.p. of the trimethyl-ester was 124°; mixed with the trimethyl-ester of the acid from actinodaphnine it softened at 124° and melted at 127-128°, so there was no actual depression.

(d) Oxidation of O-methyl-actinodaphnine: By oxidation of O-methyl-actinodaphnine with potassium permanganate m-hemipinic acid was obtained. The oxidation was carried out as described for diethyl-boldine (see page 71). The m-hemipinic acid was identified as its ethylimide, mixed with an authentic specimen/

specimen it did not show a depression of its m.p. 230.5°.

(7) Formation of dicentrine by methylation of actinodaphnine: The oily O-methyl-actinodaphnine was dissolved in acetone (70 c.c.) and methyliodide (4 c.c.) added. After 20 hours the crystals which had separated were filtered off and dried (2.35 gm.). They were dissolved in a large amount of water, made alkaline with potassium hydroxide and extracted with ether, Thus tertiary and unchanged secondary base were separated from quaternary salt. The ether left on evaporation an oil (1.125 gm.) which was dissolved in freshly distilled acetic anhydride (8 c.c.) and left at room temperature for 7 hours. Water (60 c.c.) and concentrated HCl (6 c.c.) were added, after complete decomposition of the acetic anhydride the solution was repeatedly extracted with large amounts of ether to remove the acetyl compound of the secondary base which had escaped methylation. The ether solution was repeatedly washed with sodium hydroxide, dried over $CaCl_2$ and evaporated; the crystalline residue/

residue of O-methyl-N-acetyl-actinodaphnine (0.527 gm.) was recrystallised from little ethyl alcohol, m.p. 222-224° (blue fluorescence in alcohol and ether).

4.158 mg. subst. 10.435 mg. CO_2, 2.285 mg. H_2O

$C_{21}H_{21}O_5N$ Calc. C = 68.66, H = 5.72

Found C = 68.44, H = 6.11.

The solution after the removal of the O-methyl-N-acetyl-actinodaphnine was made alkaline with potassium hydroxide and extracted with much ether. This left 0.343 gm. of a crystalline substance which after two recrystallisations from alcohol melted at 169°.

3.971 mg. subst. 10.30 mg. CO_2, 2.16 mg. H_2O

2.676 mg. subst. 0.106 c.c. N 758 mm./19°.

$C_{20}H_{21}O_4N$ calc. C = 70.79, H = 6.19, N = 4.13

found C = 70.74, H = 6.09, N = 4.62

Dicentrine, kindly supplied by Professor Asahina and Dr Manske had the same m.p., a mixed melting point did not show a depression. The intermediate products of the Hofmann degradation (methine and vinyl product) were then compared with authentic specimens from dicentrine and found to be identical.

(8) /

(8) Derivatives of O-ethyl-actinodaphnine: In the same way as described above for dicentrine O-ethyl-N-methyl actinodaphnine (a) (with diazoethane and methyl iodide) and O-ethyl-N-ethyl-actinodaphnine (b)(with diazoethane and ethyl iodide) were prepared.

(a) Recrystallised twice from alcohol, m.p. 198-199°, rather sparingly soluble in alcohol.

4.008 mg. subst. 10.51 mg. CO_2, 2.35 mg. H_2O

$C_{21}H_{23}O_4N$ (V) Calc. C = 71.38, H = 6.51.

Found C = 71.51, H = 6.56

(b) Recrystallised twice from ethyl alcohol, m.p. 213-214°, fine needles with strong refraction, sparingly soluble in alcohol (0.168 gm. dissolve in 40 c.c. of boiling alcohol).

4.102 mg. subst. 10.825 mg. CO_2, 2.41 mg. H_2O

$C_{22}H_{25}O_4N$ Calc. C = 71.93, H = 6.81

Found C = 71.97, H = 6.57

In analogy to the preparation of dicentrine O-ethyl-N-acetyl-actinodaphnine was obtained as a by-product; it was recrystallised from dilute alcohol, but/

but could not be obtained in an analytically pure state. As already mentioned there is some evidence of N-methyl-actinodaphnine occurring naturally, a Hofmann degradation was therefore effected on O-ethyl-N-methyl-actinodaphnine in the way described above for O-methyl-N-methyl-actinodaphnine dicentrine.

O-ethyl-actinodaphnine-methine was recrystallised from little alcohol; after three recrystallisations it melted at 142-144°.

4.070 mg. subst. 10.86 mg. CO_2, 2.375 mg. H_2O

$C_{22}H_{25}O_4N$ Calc. C = 71.93, H = 6.81

Found C = 72.77, H = 6.53

The methine base was converted into the quaternary iodide and trimethylamine split off by means of potassium hydroxide; the crystalline vinyl product which separated was extracted with chloroform and recrystallised twice from alcohol, m.p. 186-187°.

3.985 mg. subst. 10.785 mg. CO_2, 1.965 mg. H_2O

$C_{20}H_{18}O_4$ Calc. C = 74.53, H = 5.59

Found C = 73.81, H = 5.52

(9) Positions of the CH_3O- and OH- groups in ring B:

O-ethyl-N-methyl-actinodaphnine (VII, 0.095 gm.), phloroglucinol (0.095 gm.), concentrated sulphuric acid/

acid (0.67 gm.) and water (1.2 c.c.) were heated to gentle boiling for 5 minutes, the reaction mixture was afterwards heated on the water-bath for 6 hours. Boiling water (14 c.c.) was added, the bulky precipitate of dark red phloroglucinol condensation products was filtered off and the aqueous solution extracted with ether for 12 hours. The acid solution was neutralised with sodium bicarbonate and rapidly extracted with much ether. The ethereal solution was dried over potassium carbonate, leaving behind 40 mg. of the beautifully crystalline dihydroxy compound (X). Colourless crystals, decomposing from about 160°, giving only a slight precipitate with Mayer's reagent. Ferric chloride reaction in alcoholic solution dark blue, slowly turning into dark green.

The dihydroxy compound (40 mg.) was dissolved in a few drops of methyl alcohol and an ethereal solution of diazomethane added. After standing for ten hours, the methylation products were worked up as usual, yielding 30 mg. of non-phenolic base which was an oil (XI). The solution of this base in hydrochloric acid gave a bulky precipitate with Mayer's reagent.

The oily base was dissolved in a few drops of acetone/

acetone and a few drops of methyl iodide were added. After standing for 9 hours the acetone and the excess methyl iodide were removed under reduced pressure; the quaternary iodide proved very difficult to crystallise. It was therefore dissolved in water (5 c.c.), solid caustic potash was added and the solution was refluxed for an hour. Isolated by extracting with ether, the methine base was a yellow oil (22 mg.) which could not be crystallised.

The yellow oil was therefore dissolved in 2 c.c. of methyl alcohol, the second step of the Hofmann degradation being effected in the same way as in the case of O-methyl-actinodaphnine-methine (di-centrine-methine, comp. pp.

The crude vinyl compound (10 mg.) was dissolved in ethyl alcohol (4 c.c.), concentrated to a volume of 1 c.c. and then 2 drops of water added, the vinyl product then crystallised spontaneously (XII). M.p. 134°, m.p. after mixing the corresponding vinyl-phenanthrene from laurotetanine (XIII, m.p. 142°) was 135° (softening at 132°).

Also/

Also the form of the crystals was exactly the same; there is extremely strong evidence that the two products are identical; owing to want of material, it was impossible to obtain a micro-analysis for product (XII). As already mentioned it is hoped to remove any doubt of the correctness of the proposed structure by synthetical experiments.

SUMMARY.

1. A complete review of the literature of aporphine alkaloids has been given.

2. It has been proved that (a) laurotetanine is 2-hydroxy-3-5-6-trimethoxy-nor-aporphine and (b) boldine is 2-6-dihydroxy-3-5-dimethoxy-aporphine.

3. It has been demonstrated that the still unknown alkaloid actinodaphnine is an aporphine base and is very likely to be 2-hydroxy-3-methoxy-5-6-methylene-dioxy-aporphine.

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Ring closure may either be effected by P_2O_5, $POCl_3$, PCl_5. Any numbers given refer to the general list of references.

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